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# Archives of Internal Medicine

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NUMBER 1

## THE HEART AND THE AORTA IN EARLY SYPHILIS: CLINICAL OBSERVATIONS.\*

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and

PAUL D. WHITE, M.D.,  
M.D.

### INTRODUCTION

The organism of syphilis invades the blood stream early in the infection, and it is generally admitted that during this period of invasion the treponemes lodge in the various viscera, including the heart and the aorta. Then follows a considerable latent period, after which symptoms and signs of syphilitic heart and aortic disease may become manifest, usually a number of years after the original infection.

Recently, however, there have been several reports emphasizing that signs of involvement of the heart and aorta in syphilis appear in the early stages of the disease. This is logical in view of the known facts pertaining to syphilitic infection, but is not well borne out in the clinical experience of many observers. Because we have felt that many of the reported cases have not been critically enough examined, we undertook the investigation described in this report.

### LITERATURE

Crassmann's<sup>1</sup> work is quoted in most articles on cardiac syphilis. In 288 cases of secondary syphilis he detected arrhythmias or pulse disturbances in 85 per cent, and murmurs in 40 per cent.

Ameling and Sternberg,<sup>2</sup> in 1924 reported that they believed Crassmann's figures were too high. They had followed 225 cases in the early stages for one year. Twenty-one per cent showed either cardiac enlargement (checked by roentgen-ray examination), altered quality of the second sound, tachycardia, extrasystoles or murmurs. One case showed an aortic regurgitation labelled by the authors as definitely syphilitic.

\* From the South Medical and Cardiac Clinics, Cardiographic Laboratory and X-Ray Department of the Massachusetts General Hospital.

1. Crassmann, L. A. *Deutsches Arch. f. klin. Med.* 60:475, 1900; *Ibid.* 60:52 and 264, 1901.

2. Ameling, W., and Sternberg, A. *Arch. f. klin. Med.* 145:34 (Sept.) 1924.

Brooks<sup>3</sup> reported that of 300 cases of syphilitic heart disease twenty-four (8 per cent) showed cardiac involvement in the secondary stage.

3. Brooks, Harlow. *Am. J. Syph.* 6:172 (April) 1914.

Two of these were proved by postmortem examination. Brooks<sup>4</sup> has also reported two cases of aortic aneurysm developing within six months of the primary lesion. He regards tachycardia, extrasystoles, precordial pain, palpitation, dyspnea, apical systolic murmurs, cyanosis, and a state of apprehension as indicative of the possibility of heart damage in the early stages. The most frequent pathologic lesions consisted in perivascular infiltrations around the coronary arteries and their branches resulting in myocardial damage. Brooks believes that involvement of the heart may be noted early and may end fatally or may remain long quiescent.

Moore<sup>5</sup> agrees with Brooks in believing that the heart may early show signs of involvement. He reports a case of a male, aged 24, with a positive Wassermann reaction and a beginning macular rash, who had had precordial pain for a few days. His temperature was 99.6 degrees and the pulse was 110. There was a slightly enlarged area of cardiac dullness, an occasional extrasystole, and a soft systolic murmur at the base. With antisyphilitic therapy the symptoms subsided.

Hazen<sup>6</sup> states that myocardial disturbances may occur. He quotes a case that developed a serious myocarditis before the secondary stage. According to Hazen, if myocarditis develops during the secondary stage, "the principal features are arrhythmia, particularly intermittence and tachycardia, and at times extrasystoles. The irregularity becomes more marked after mild exercise or through nervous fear. Precordial pain is not common, and various writers disagree as to the amount of dyspnea present. Cyanosis frequently occurs."

Engman<sup>7</sup> believes that myocarditis, valvular disease, and aortitis begin during the early invasive stage, although there may be no symptoms until later. Acute symptoms, such as arrhythmia and precordial pain, occur during the primary and secondary periods but are of short duration. Subacute aortitis is not uncommon.

Wiltshire<sup>8</sup> says that cardiac arrhythmia is often noted in the secondary stage, but that the pericardium and endocardium are rarely affected.

Liek<sup>9</sup> reports a case of aortic dilatation interpreted by roentgen-ray examination developing seven months after the primary lesion.

Howard<sup>10</sup> states that of fifty syphilitic patients in the secondary stage, eight complained of palpitation, five of cardiac pain, and three of dyspnea. One had edema. Cardiac dilatation may often be made out,

4 Brooks, Harlow. *Am J M Sc* **146** 513, 1913.

5 Moore, W. C. *Am J M Sc* **160** 660 (May) 1918.

6 Hazen, H. H. *Syphilis*, 1921, p. 205.

7 Engman, M. F. *Nelson's Loose-Leaf System of Medicine* **2** 290.

8 Wiltshire, H. *Tr. West London Med-Chir Soc.*, 1922.

9 Liek. *Fortschr. a. d. Geb. d. Röntgenstrahlen* **17** 23, 1911.

10 Howard, T. *Am J M Sc* **167** 266 (Feb) 1924.

Howard says, together with occasional extrasystoles and frequently a reduplicated second sound at the apex. A case is cited of a man, aged 20, who had a primary lesion three months before coming under observation. On admission he had had palpitation and precordial pain for from six to eight weeks. There was an apical systolic murmur. The right border of dulness was 3 cm from the midsternum, the left border of dulness was 17 cm from the midsternum and in the anterior axillary line. The second sound was reduplicated at the apex. Rest and mercury cured the symptoms in one month, and the transverse diameter of the heart decreased from 20 to 15 cm.

Boyd,<sup>11</sup> in a review of 4,000 necropsies, found a beginning aneurysm in a case with primary syphilis.

Oddo and Mattei<sup>12</sup> quote Fournier as finding disturbances of the heart rhythm frequently in cases of secondary syphilis. According to these authors, cardiac syphilis in the secondary stage of the disease is not infrequently fatal. They recognize two classes of patients with heart lesions in secondary syphilis: those with the "benign" arrhythmias, and those in whom the cardiac syphilis takes a "malignant" form with rapid decompensation and ultimate death. A case is cited as of pericarditis due to syphilis in the secondary stage that was obviously a case of coronary thrombosis—from the standpoint of history, course, physical and postmortem findings.

Bonnin<sup>13</sup> states that Etienne had seen cases of syphilitic aortitis appearing nine, eight, and even three months after the chancre. Symptoms of aortitis are, however, according to Bonnin, rare in the first year of the infection.

Vaquez<sup>14</sup> cites a case that he had seen in a girl of 20 with secondary syphilis who developed a permanently slow pulse with Adams-Stokes' attacks, presumably on a syphilitic basis.

Not all observers, however, believe that evidence of cardiac damage is common in the early stages of syphilis. Cohn<sup>15</sup> says that "syphilis rarely causes detectable damage to the heart in the primary and secondary stages."

Wilson, Wile, Wishart and Herrmann,<sup>16</sup> at the conclusion of a report concerning the electrocardiographic changes following arsphenamine treatment of cardiac and aortic syphilis, state, "In twenty patients with primary and secondary lues intensive arsphenamine treatment produced no electrocardiographic abnormalities. A study of about sixty

11 Boyd, L. J. *Am J M Sc* **168** 654 (Nov.) 1924

12 Oddo, C., and Mattei, C. *Arch d mal d cœur* **13** 289 (July) 1920

13 Bonnin, H. *Medecine* **7** 156, 1925

14 Vaquez, H. *Diseases of the Heart*, 1924, p. 319

15 Cohn, A. E. *Nelson's Loose-Leaf System of Medicine* **4** 333

16 Wilson, F. N., Wile, U. J., Wishart, S. W., and Herrmann, G. R. *Proc Soc Exper Biol & Med* **23** 275, 1926

patients with primary and secondary lues has convinced us that reliable clinical or electrocardiographic evidence of involvement of the heart or aorta during this stage of the disease is decidedly rare "

Marvin,<sup>17</sup> who in 1920 began an investigation at the Massachusetts General Hospital similar to ours, reports that he saw thirty-six patients with a primary lesion of several weeks' duration or early secondary manifestations. The number of visits made by each patient did not exceed five in any case and in most instances was less than that. Each patient was examined at each visit as to the size of the heart, rhythm, murmurs, cyanosis and so on, and was questioned as to the occurrence of any symptoms. Several patients with asymptomatic rheumatic heart disease were excluded. The results were absolutely negative. There were no symptoms, murmurs or irregularities. Although one patient had occasional auricular premature beats, it was found that they had been noted on an earlier medical record before the patient had acquired the syphilitic infection.

#### PRESENT OBSERVATIONS

*Selection of Cases*—The basis for the present report is a series of fifty cases of primary and early secondary syphilis seen in the South Medical Department of the Massachusetts General Hospital in the spring of 1926. These cases were studied by means of a complete cardiac history and a thorough physical examination of the heart, supplemented in every instance by roentgen-ray and electrocardiographic study.

Considerable care was used in the selection of cases. It was felt that some of the confusion in the past had resulted from lack of care in excluding other forms of heart disease—for example, rheumatism or arteriosclerosis—in the patients studied, and from ascribing the signs and symptoms found to the syphilitic infection. Six patients were discovered with mitral stenosis presumably of rheumatic origin, and these were excluded from our series. Five of these six cases had an accompanying mitral regurgitation, and two had in addition an aortic regurgitation, in all cases asymptomatic.

No patients over 40 years of age were included in the series. This selection was for the purpose of preventing so far as possible the complications of coronary sclerosis. While realizing that no age limit artificially set is of absolute value, we felt that this form of selection would aid materially in ruling out this complication. In addition each case was examined to determine the condition of the radial and brachial artery walls and the retinal vessels. No cases of arteriosclerosis in these localities were found. There was no arcus senilis present in any

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17 Marvin, H. M. Personal communication to the authors.

case We were prepared to exclude any cases of essential hypertension but none were found

Because we realized the rôle played by the cardiac neuroses in the symptomatology of the cardiovascular apparatus, an estimate was made in each case of the mental attitude of the patient, but no cases of true neurosis were discovered One patient with an enlarged thyroid and associated cardiac symptoms was excluded from the series

Finally, an effort was made to exclude all cases complicated by other conditions than syphilis The most frequent complications found were gonorrhea and pregnancy In other words, the series was made to include so far as possible cases with a syphilitic infection only Nevertheless, there are included in the fifty, one patient with a mild diabetes, one with gonorrhea, one with tuberculosis, and one pregnant woman These four cases gave an absolutely negative cardiovascular study<sup>18</sup>

*Age, Sex, Race and Occupation*—There were nineteen females and thirty-one males in this series The ages varied from 16 to 34 years The age distribution is given in table 1

TABLE 1—*Age Distribution in Fifty Cases*

Age	Cases	Age	Cases	Age	Cases
16 years	1	22 years	3	29 years	3
17 years	2	23 years	5	30 years	1
18 years	3	25 years	4	31 years	3
19 years	2	26 years	3	32 years	3
20 years	2	27 years	2	34 years	3
21 years	9	28 years	1		

Forty-seven of the patients were white and three were colored Thirty-four of the white patients were born in the United States Five patients were Italian, one was Scotch, one Irish, one Armenian, one Finnish, one Swiss, two Swedish, and one Russian

The occupations showed the usual variations

*Family History of Cardiovascular Disease*—In seven cases there was a history of cardiovascular disease in the family In five instances death came in middle or advanced age from "shocks" or "heart failure" The remaining two patients were sisters of the patients who died in the twenties of "heart disease," probably rheumatic

*Past History*—The incidence of rheumatic fever, chorea, tonsillitis, scarlet fever and diphtheria was recorded in each case Twenty-one patients gave a positive history Of these, eleven had had tonsillitis or frequent sore throats alone Three had had scarlet fever alone Two

18 It is of interest to note that in twenty-three congenital syphilitic infants and children under the age of 5 years who came to necropsy at the Massachusetts General hospital during the last fifteen years no macroscopic evidence of syphilitic involvement of heart or aorta was noted

gave a history of diphtheria alone and one of these was questionable. An additional one had had diphtheria and occasional severe sore throats. One patient gave a history of scarlet fever, diphtheria and a tonsillectomy. In one instance there was a questionable attack of rheumatic fever ten years before. Two patients had had diphtheria with a questionable rheumatic infection.

Only five patients had experienced any possible cardiac symptoms prior to the present illness, and these were mild in nature. In one case there was moderate shortness of breath associated with a rapid gain of a large amount of weight since discharge from the army. Another patient complained of palpitation whenever she was nervous. One had had an "irregular heart" previous to a tonsillectomy eight years before at the age of 13, with no symptoms since the operation. Two patients gave a history of premature beats, in one case associated with short stabs of pain beneath the lower sternum.

Nineteen patients had passed life insurance or army examinations within a few years before the onset of the syphilitic infection.

*Syphilitic Infection and Treatment*—Eleven patients were admitted with a primary lesion. Three had both the primary and early secondary manifestations, while thirty-six were admitted during the secondary stage of the disease.

It was impossible to state definitely the duration of the infection in seventeen patients. Four patients had entered promptly (i. e., a week or less) after discovering the primary lesion. Four others came in about two weeks after the appearance of the chancre. About a month elapsed before treatment was given in six cases. There was an interval of about two months in six cases, about three months in five cases, about four months in two, five or six months in two, eight months in one, two years in one, and in two cases several desultory injections by local physicians had been given over a period of six months to a year before intensive treatment was started at the Massachusetts General Hospital.

The duration of treatment is computed from the time the patient entered the South Medical Department to the time when he was seen by one of us. Only an approximation is possible because of the irregularity that characterizes the visits of certain patients. The duration of the treatment in the individual cases will be found in table 2, which also contains data for each case on the approximate duration of the infection before treatment, the probable duration of the infection when the patient was seen, and the amount of treatment that he had received.

The general plan of treatment for a patient appearing at the South Medical Department in the primary or early secondary stages of the infection may be broadly summarized as follows. Eight injections of an arsenical are given intravenously at weekly intervals unless signs

of toxicity from the arsenic supervene. If the patient is infectious an effort is made to have him enter the ward until the height of the infectivity is passed. While in the ward he receives arsenical injections every four days. After his discharge the treatment is the same as that outlined for the nonhospitalized patients. At the conclusion of the

TABLE 2—Summary of Cases

Case	Stage on Entrance	Duration of Syphilis Before Entry	Duration of Treatment	Amount of Treatment		Total Duration of Infection When Seen
				Injection of Arsenic	Injection of Mercury or Bismuth	
1	Secondary	1 mo +	2 mos	3	3	3 mos +
2	Secondary	3 mos ?	3 mos	8	5	6 mos ?
3	Secondary	6 mos	7½ mos	8	15	13½ mos
4	Secondary	?	9½ mos	8 + 4	15 + 2	9½ mos +
5	Secondary	2 mos +	2 wks	3	0	2½ mos +
6	Secondary	2 mos	10 mos	8 + 6	15 + 3	1 yr
7	Secondary	?	1 wk	2	0	1 wk +
8	Secondary	3½ wks	4¾ mos	8	12	7½ mos
9	Secondary	2 yrs	11 mos	8	12	2 11/12 yrs
10	Secondary	1 mo +	4 wks	4	0	2 mos +
11	Secondary	?	1 yr	10 + 4	14 + 3	1 yr +
12	Secondary	4 mos	2 mos	4	1	6 mos
13	Secondary	2 mos	1 mo	5	0	3 mos
14	Secondary	3 mos	3 mos	8	5	6 mos
15	Secondary	2 mos	1 wk	1	0	2 mos +
16	Secondary	?	8 mos	8 + 8	7 + 9	8 mos +
17	Secondary	?	2 mos	9	0	2 mos +
18	Secondary	1 yr	1 mo	5	0	13 mos
19	Secondary	?	1½ mos	6	0	1½ mos +
20	Secondary	?	1 wk	3	0	1 wk +
21	Primary and secondary	?	5½ mos	8	14	5½ mos +
22	Secondary	?	3 mos	8	8	3 mos +
23	Secondary	?	2 wks	3	0	2 wks +
24	Primary	3 wks	1 wk	2	0	1 mo
25	Secondary	5 mos	1 wk	2	0	5¼ mos
26	Secondary	1 mo	6 mos	8	15	7 mos
27	Primary	5 days	9 mos	8	21	9 mos
28	Secondary	6 mos	6 mos	8	8	12 mos
29	Primary	days	3½ mos	8	8	3½ mos +
30	Secondary	2 mos	1½ mos	3	2	3½ mos
31	Primary	3 wks	2½ mos	8	4	3¼ mos
32	Primary	2 days	4¼ mos	8	11	4¼ mos
33	Secondary	?	5½ mos	12	8	7½ mos +
34	Secondary	?	3 mos	3	11	3 mos +
35	Secondary	?	1 wk	3	0	1 wk +
36	Secondary	3 mos	4 mos	8	11	7 mos
37	Secondary	?	3 mos	8	1	3 mos +
38	Primary	2 wks	2½ mos	10	1	3 mos
39	Primary and secondary	?	2 wks	3	0	2 wks +
40	Secondary	4 mos	4 mos	8	2	8 mos
41	Secondary	3 mos	3 days	1	0	3 mos
42	Primary and secondary	days	1 mo	6	0	1 mo +
43	Secondary	7½ mos	5½ mos	8	7	13 mos
44	Primary	2 wks	1 mo	7	0	1½ mos
45	Secondary	1½ mos	4½ mos	8 + 8	4	6 mos
46	Primary	2 wks	1 mo	6	0	1½ mos
47	Secondary	1½ mos	2¼ mos	8	0	4 mos
48	Primary	2 wks	10½ mos	8 + 6	15 + 9	11 mos
49	Primary	2 mos +	6 mos	8	12	8 mos +
50	Primary	?	10 days	3	0	10 days +

couse of arsenic therapy, fifteen intramuscular injections of mercury or bismuth are given at weekly intervals. After a rest period of six weeks the patient returns for a Wassermann test. If the test is positive the whole couse of treatment is gone through again. If the test is negative six injections of an arsenical solution and ten or twelve of

the mercury or bismuth are given. From this point the treatment varies, but as no patient included in this series had received more than the amount outlined above, a further discussion is unnecessary.

*Cardiac Symptoms Since Onset of Syphilis*—Two patients complained of occasional symptoms of palpitation probably due to extrasystoles, and in addition one of these patients at times had short stabs of pain beneath the lower sternum. In both patients these symptoms had been present for months before the acquired syphilitic infection. Another patient in answer to the routine questions stated that her feet and ankles were swollen at night, but on examination the heart was found to be in excellent condition and the local signs due to moderately developed varicose veins.

#### PHYSICAL EXAMINATION

The temperature was normal in all cases. As mentioned before no case showed an arcus senilis, and in all the eye-grounds were normal. No cases showed any abnormal pulsations, a tracheal tug, friction rubs, or evidence of congestive failure, including cyanosis and edema. The knee jerks and pupil reactions were likewise normal.

One of the most frequently reported signs of early cardiac involvement in syphilis stressed by certain authors is pulse irregularity. The pulse was regular in 39 of our cases. Nine other cases were regular except for sinus arrhythmia. Infrequent extrasystoles were found in two patients and in these cases the irregularity was not noticed by the patient. In neither of these cases were the premature beats present in the electrocardiographic tracings. The rate varied considerably. One patient showed a bradycardia of 50 that later mounted to 65 with the nervousness associated with having an electrocardiogram taken. There was no evidence of block in this case, and it probably represents a sinus bradycardia. Five cases had a rate of 60. Ten more had rates between 61 and 70. In twenty-three the rate was from 71 to 80. In seven the rate was from 81 to 90. And in two apprehensive subjects the rate ranged between 90 and 110. The form of the pulse was not remarkable, and in all cases the radial pulses were equal and synchronous. The radial and brachial artery walls were soft, and there was no capillary pulse.

In all cases the midclavicular line was used as the standard for the maximum left border of dulness and position of the apex impulse. In one case the left border of dulness to percussion was 1 cm. outside the midclavicular line. This case will be discussed later. With this one exception, the percussion outlines were normal.

The sounds were of good quality and normal in most cases. Two cases mentioned above under the consideration of the pulse showed rare

premature beats. A split pulmonic second sound was noted in two cases. Another case had a split first sound at the apex.

In three cases a soft transient systolic murmur was present at the apex. The murmur in these cases was markedly influenced by respiration and by change in position. It was never transmitted. In one other case a similar murmur was heard at the base of the heart. In the case mentioned above that showed the abnormal percussion dulness murmurs were found that will be described later.

The blood pressure findings were not important enough to summarize. There were no cases of hypertension. The highest pressure noted was 136 systolic, 80 diastolic. One third of the cases had systolic pressures between 100 and 110. Two cases gave systolic readings of 90 to 95.

#### LABORATORY EXAMINATIONS

*Wassermann Test*—Either a Wassermann test or a dark field examination or both is made on each patient on entry. In only three cases of the series had no Wassermann test been made. It was positive in the last test at the time the patient was seen in thirty-three cases. In nine cases it had been positive but had become negative at the time the patient was seen. In five cases the Wassermann reaction had never been positive during the time the patient was receiving treatment. These were cases in which the diagnosis had been made by dark field examination on entrance, and in which the first course of treatment had not been completed.

*Blood and Urine Tests*—These tests were not done on all patients. Blood counts and smears were made in only five, all of which were negative. Urine tests were made in twenty-three cases and were normal in twenty-one, one case showed some pus cells and the other, the diabetic case referred to early in the report, showed persistent traces of sugar.

*Spinal Fluid Test*—The spinal fluid was examined in only one case. This spinal fluid gave a positive Wassermann reaction which eventually became negative under treatment.

#### ROENTGEN-RAY EXAMINATIONS

Teleoroentgenogram heart plates were taken of all patients. The roentgen-ray report was completely negative in thirty-one cases. One case that will be discussed later was slightly abnormal. In two patients, both short, obese persons, a high diaphragm caused a relative increase in the transverse diameter of the heart. In two cases the aortic pulsations as seen by the fluoroscope were slightly more prominent than usual. Four cases were described as having very slight prominence in the region of the aortic arch, but the cardiac measurements were within normal limits and no cardiac lesion was supposedly present. Three

cases were described as having a slightly prominent left ventricle, with measurements within normal limits. In five cases the notation was made that the transverse measurements of the heart were slightly beyond the maximum normal. This is assuming a standard of half the intrathoracic diameter for the maximum normal transverse measurement. According to Smith and Bloedorn,<sup>19</sup> the normal standard for the maximum cardiothoracic ratio is 57 per cent. All these five cases showed measurements exceeding only very slightly 50 per cent of the intrathoracic diameter, and in no case was this figure as high as 57 per cent. Another patient was described as having slight enlargement of the cardiac shadow downward and to the left as well as slight prominence of the right auricle. The last observation is very questionable and the transverse diameter of the heart was 12 cm. in a chest of 23.5 cm. The final patient was described as having a slightly prominent left auricle and pulmonary artery, but in this case a slight thoracic rotation to the right rendered too rigid an interpretation of the shadow impossible.

#### ELECTROCARDIOGRAMS

The electrocardiographic tracings were completely negative in thirty-five cases except for some sinus arrhythmia and somatic tremor in certain ones of this group. The other sixteen cases also were normal, but exhibited certain slight and unimportant variations. Two cases had sino-auricular tachycardia with rates around 120 per minute. One of these cases and four other cases showed questionable or slight abnormal right axis deviation. A pregnant woman showed slight abnormal left axis deviation. The other findings may be summarized as follows:

- Case 9 Left axis deviation, index plus 16, angle minus 30 degrees,  $P_2$  plus 4 mm,  $P_3$  plus 3 mm
- Case 12  $P_2$  plus 4 mm
- Case 15  $P_2$  plus 3 mm
- Case 22  $P_2$  plus 3 mm
- Case 45 Very high Q-R-S in leads II and III
- Case 47 Normal rhythm, rate 52, P-R interval 0.18 seconds, somatic tremor, sino-auricular bradycardia
- Case 48 Questionable variation of the sino-auricular pacemaker
- Case 49  $P_2$  plus 3 mm,  $T_2$  plus 8 mm

#### COMMENT

Forty-nine of the fifty cases in this series were normal or exhibited minor variations, principally in the roentgen-ray examination or electrocardiogram, which could not be ascribed to any pathologic process. It should be pointed out that all of these slight abnormalities may occur in persons who are perfectly normal in every other way. The burden of the proof must rest on those who would give a syphilitic basis for their interpretation.

<sup>19</sup> Smith, H. W., and Bloedorn, W. A. U. S. Nav. M. Bull. **16** 219 (Feb.) 1922

The one case that may be regarded as possibly pathologic may be summarized as follows

CASE 3—A man, an Italian grocery clerk, aged 23, entered the South Medical Department, June 25, 1925. He gave a history of having had a penile sore in January, 1925. At entrance he showed a scar on the frenum, alopecia, generalized adenopathy, a macular rash, and mucous patches in the throat. The duration of the secondary manifestations was not ascertained. Treatment was immediately instituted and by the time he was seen by one of us, Feb 16, 1926, he had received eight injections of arsphenamine, and fifteen intramuscular injections of mercurial oil and bismuth quinine iodide. His Wassermann reaction was strongly positive at the time of entrance but had become negative six months later. A single urine examination four months after the treatment was started was negative. His family and past histories were negative from a cardiovascular standpoint. He had had no cardiac symptoms since the onset of the syphilitic infection.

The temperature was normal. There was no cyanosis or edema. The pupils reacted normally and the knee jerks were equal and active. The eyegrounds were negative. The artery walls were soft. The pulse rate was 80, regular, equal and synchronous, and rather full. There were no thrills, or abnormal pulsations and no tracheal tug. The apex impulse was in the fifth left interspace 9 cm from the midsternal line. The midclavicular line was 8 cm. The left border of dulness was 9.5 cm to the left of the midsternal line, the right border of dulness 3.5 cm. The dulness in the second space was 6 cm wide. When examined in the sitting position there was no Broadbent's sign. The heart sounds were normal at the apex. The rhythm was regular and the rate about 80-90. There were no murmurs at the apex, but a slight systolic murmur was heard in the pulmonic area. No important change occurred in the recumbent position. After exercise and while he was recumbent the pulmonic systolic murmur was slightly increased but still was not loud. A short apical systolic murmur appeared. No diastolic murmurs were present. The heart shifted well with changes in position.

The electrocardiogram showed normal rhythm with a rate of 90. The roentgen-ray report was: The heart shadow was definitely increased in all diameters. The greatest prominence was to the left in the region of the left ventricle. There also was some prominence of the pulmonary arteries. Supracardiac dulness was increased but this was probably due to the dilatation of the pulmonary arteries. In the oblique view the shadow of the aorta appeared normal. There was slight general enlargement of the heart. The measurements were: right, 4 cm, left, 10.1 cm, transverse, 14.1 cm, longitudinal, 15.5 cm, base, 12.2 cm, great vessels, 6.9 cm, chest, 26 cm. There appeared to be a slight thoracic rotation in the roentgen-ray examination that might account for the small variation between the percussion measurements and those of the roentgenogram, as well as for the prominence in the region of the pulmonary artery. The cardiothoracic ratio was 54 per cent, or well within Smith and Bloedorn's normal limits.

We do not believe that this case can justly be labelled syphilitic heart disease on the basis of the slight and unimportant abnormalities exhibited.

#### SUMMARY AND CONCLUSIONS

A careful study of fifty cases of early syphilis at the Massachusetts General Hospital by history, physical examination, roentgen-ray examination and electrocardiogram showed no definite clinical evidence of disease of the heart or aorta in any case. A study of the literature shows that clinical evidence of cardiovascular disease in early syphilis is rare.

# ALTERATIONS IN THE PERMEABILITY OF SKIN CAPILLARIES DURING PREGNANCY AND PUERPERIUM \*

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AND

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CHICAGO

Pregnancy and parturition offer an interesting field of observation, quite apart from purely obstetric considerations, because of the pronounced differences that occur in resistance to certain infectious diseases as well as other clinical conditions during the period of gestation and the puerperium. The change in the resistance to tuberculosis illustrates this very well.

That menstruation in itself is detrimental in tuberculosis is well known. The statement that the tuberculous woman "is killed by her menstruation" has often been repeated, and while mere repetition by no means carries conviction, there seems little doubt that careful clinical observation gives a firm basis for the belief. The biologic changes of the menstrual cycle, endocrine in origin, involve a profound alteration of the autonomic status of the organism and are associated, seemingly, with a definite ionic rearrangement. These metabolic changes are likewise associated with an increase in permeability of the vascular endothelium (observed in the meninges by Heilig and Hoff,<sup>1</sup> by Benda,<sup>2</sup> and by us in the capillaries of the skin<sup>3</sup>).

Pregnancy, the consensus of opinion would indicate, does not involve the necessary activation of a quiescent tuberculous focus. But in a certain number of cases there seems to be an increase in the lability of the lesions. This may be due to the increase in the enzyme content of the tissues and plasma, an increase that is only partially balanced by a simultaneous increase in antiferment<sup>4</sup>.

Parturition, without doubt, is injurious. Is it the physical effort, or is it the general biologic alteration of the organism associated with such changes as the involution of the uterus, or the beginning of lactation,

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1 Heilig, R, and Hoff, H. *Klin Wchnschr* **3** 2049 (Nov 4) 1924.

2 Benda, Robert. *Munchen med Wchnschr* **72** 1686 (Oct 2) 1925.

3 Petersen, W F, and Milles, George. The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, *Arch Int Med* **38** 730 (Dec) 1926.

4 Petersen, W F. Resistance to Tuberculosis, *Arch Int Med* **21** 14 (Jan) 1918.

that influences the resistance to tuberculosis so unfavorably? During involution proteolytic enzymes are swept into the circulation in quantity, at a time when the antiproteolytic property of the plasma diminishes. While the calcium balance has been studied, the results are conflicting and as practically all the work has been done without reference to the potassium metabolism, the results are of relatively little use to us.

In the observations here recorded we have made use of the simple blister method described elsewhere in this series of articles.<sup>5</sup> We have made observations on about 100 women, most of them normal term or postpartum cases. The details have been recorded in tables 1 to 5.

CHART 1—*White Women, Antepartum*

Num ber	Race	Age	Par- ity	Clinical Diagnosis	Albu min	Blood Pres sure	Blister Time in Hours	Serum Pro tein, per Cent	Blister Pro tein, per Cent	Ratio B/S	R/T
30	W	35	I	Term—with mechanical ileus, induced labor, spontaneous delivery (repeated tonsillitis, tonsillectomy, appendectomy, cholecystectomy)	—	110/68	8	7.10	4.78	0.61	8.0
31	W	22	VIII	Antepartum (has had scarlet fever, rheumatism, pneumonia, tonsillectomy)	—	115/70	?	8.06	5.49	0.68	
32	W	30	V	Term	—	125/80	4½	8.06	5.50	0.68	15.0
33	W	35	VIII	Term	—	118/80	9	7.63	5.29	0.69	7.6
34	W	18	I	Term	—	118/80	5½	7.76	5.40	0.69	12.5
35	W		VIII	Term	—	142/92	5	7.84	5.09	0.69	11.0
36	W	24	I	Term	—	112/60	11	8.26	5.80	0.70	6.3
37	W	19	I	Seventh month			8	8.00	5.80	0.72	9.0
38	W	28	II	Term			5½	7.00	5.04	0.72	13.0
39	W	25	II	Term			5	8.07	5.90	0.73	14.6
40	W	35	IV	Term			6	8.06	6.06	0.75	12.5
41	W	19	I	Term	—	120/80	?	7.20	5.50	0.76	
42	W	23	I	Eighth month			5	7.05	5.49	0.78	15.6
42b	W	23	I	Term			6	6.22	4.89	0.78	13.0
43	W	20		Eighth month (casts)	+	165/98	?	7.63	6.10	0.80	
44	W	31	V	Third month, hematemesis			5½	7.20	5.90	0.82	15.0
Average										0.725	

## COMMENT

Including all cases the antepartum group has an average permeability ratio of 70.7, with practically no differences between the white and colored groups. The ratio for the postpartum group is 73.6.

A difference in the rate of blister formation seems to exist between the white and colored groups after parturition, the average time of blister formation for the white women being five and one-half hours for the colored seven hours. As the majority of these observations had of necessity, to be made by nurses busy with routine work, we are unable to place much reliance on the accuracy of these records.

<sup>5</sup> Petersen, W. F., and Willis, D. A. Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* **38**: 663 (Nov.) 1926.

CHART 2—Colored Women, Antepartum

Num ber	Race	Age	Par- ity	Clinical Diagnosis	Albu- min	Blood Pres- sure	Blster Time in Hours	Serum Pro- tein, per Cent	Blster Pro- tein, per Cent	Ratio B/S	R/T
45	C	18	I	Ninth month	—	118/78	5	7 10	4 00	0 57	11 0
46	C	21	IV	Term	—	120/92	?	7 63	4 53	0 60	
66	C	20	I	Term	—	130/90	?	7 85	4 89	0 62	
47	C	21	I	During labor	—	110/70	6	7 76	5 00	0 64	10 6
48	C	33	IV	Term	—	110/70	?	8 06	5 57	0 69	
49	C	15	I	Seventh month			6½	6 98	4 89	0 70	10 7
50	C	29	III	Term		100/60	?	8 26	6 00	0 72	
51	C	21		Term			5	7 63	5 49	0 72	14 4
52	C	18	I	In labor 24 hours			8	7 30	5 29	0 72	9 0
53	C	19	I	Eighth month			?	7 41	5 50	0 74	
54	C	16	I	Term			?	7 41	5 49	0 74	
55	C	17	I	Term		115/70	?	7 20	5 40	0 75	
56	C	21	III	Term			7	7 47	5 60	0 75	10 7
57	C	31	III	Term			5	7 05	5 29	0 75	15 0
58	C	25	II	Term			6	7 76	5 90	0 76	12 6
57	C	37		Abortion, third month			10	7 16	5 50	0 76	7 6
60	C	20	I	Term			6	7 15	5 54	0 77	13 0
61	C	25	I	Term (casts)	+	150/100	?	7 00	5 94	0 77	
62	C	20	IV	Term			5½	8 28	6 40	0 78	14 2
63	C	18	I	Term			5	7 55	6 00	0 80	16 0
64	C	20	II	Eighth month	—	110/70	10	6 76	5 41	0 80	8 0
65	C	30		Fifth month (threatened miscarriage)			5¼	6 70	5 35	0 80	15 2
Average										0 70	

CHART 3—White Women, Postpartum

Num ber	Race	Age	Par- ity	Clinical Diagnosis	Albu- min	Blood Pres- sure	Blster Time in Hours	Serum Pro- tein, per Cent	Blster Pro- tein, per Cent	Ratio B/S	R/T
1	W	28	V	Postpartum 1 day (during pregnancy, headaches, scotoma, edema of legs)	+	130/95	6	7 20	4 68	0 65	12 0
1B	W	22	III	Postpartum 4 days			7	8 28	5 69	0 68	9 7
2	W	22	IV	Normal postpartum			8	6 47	4 40	0 69	8 6
2B	W	33	III	Normal postpartum							
				postpartum 5 days			8	7 85	5 49	0 70	8 7
3	W	23	II	Normal postpartum			6	8 28	5 70	0 70	11 6
3B	W	37	VI	Normal postpartum							
				postpartum 2 days			7¼	6 55	4 57	0 70	9 7
4	W	35	VII	Normal postpartum			6	6 98	4 99	0 71	12 0
4B	W	21	I	Normal postpartum, (twins) postpartum 2 days							
							6¼	6 98	5 00	0 71	11 3
5	W	31	III	Normal postpartum			5¼	7 70	5 50	0 71	13 5
5B	W	26	VI	Seventh month pregnancy, postpartum 4 days							
							8	7 20	5 20	0 72	9 0
6	W	18	I	Normal postpartum			5½	7 30	5 29	0 72	13 0
7	W	31	IV	Normal postpartum			6½	7 63	5 70	0 74	11 3
7B	W	18	I	Normal postpartum, postpartum 5 days							
							7¼	7 20	5 35	0 74	10 2
8	W	30	III	Normal postpartum, postpartum 5 days							
							5½	7 20	5 60	0 77	10 8
9	W	35	VIII	Normal postpartum, postpartum 5 days							
							4	7 63	5 90	0 77	19 2
11	W	21		Postpartum eclamptic			?	6 72	5 30	0 78	
11B	W	39	V	Postpartum 5 days			5	7 50	6 00	0 80	16 0
12	W	19	I	Normal postpartum		108/68	5	7 00	5 80	0 83	16 6
13	W	29	III	Normal postpartum			4	6 55	5 49	0 83	20 7
14	W	23	III	Postpartum, psychosis			4	6 76	5 69	0 84	21 0
Average										0 735	

Average permeability of all antepartum cases

70 7

Average permeability of all postpartum cases

73 6

CHART 4—Colored Women, Postpartum

Num ber	Race	Age	Par ity	Clinical Diagnosis	Albu min	Blood Pres sure	Blister Time in Hours	Serum Pro tein, per Cent	Blister Pro tein, per Cent	Ratio B/S	R/T
14B	O	20	i	Postpartum 9 days			13	8.28	5.20	0.63	4.8
15	O	23		Postpartum (albumin and casts)		116/90		5.35	3.55	0.66	
16	O	23	ii	Postpartum			7½	8.49	5.80	0.68	9.0
17	O	26	v	Postpartum			7½	7.85	5.50	0.70	9.3
18	O	31	ii	Postpartum			8	5.70	5.70	0.70	8.7
19	O	28	iv	Postpartum			6¾	7.11	5.10	0.70	10.3
20	O	21	i	Postpartum			9¼	1.89	1.89	0.70	7.5
21	O	32		Postpartum			8¼	7.71	5.50	0.71	8.6
21B	O	19	i	Postpartum 5 days			5¼	8.60	6.10	0.71	13.5
22	O	18	i	Postpartum (twins) hyperten sion			5	6.22	4.47	0.72	14.4
22B	O	30	iv	Postpartum 3 days			6	7.85	5.70	0.72	12.0
22C	O	17	i	Postpartum 8 days			7	7.77	5.69	0.73	10.1
23	O	16	i	Postpartum			6¾	6.88	5.09	0.74	11.0
24	O	20	iii	Postpartum			6½	7.34	5.43	0.74	11.4
25	O	25	ii	Postpartum			8¾	7.11	5.50	0.74	8.4
25B	O	27	vii	Postpartum 4 days			8	7.10	5.29	0.74	9.2
26	O	21	i	Postpartum			7½	8.60	6.50	0.75	10.0
26B	O	20	iii	Postpartum 5 days			7	7.85	5.80	0.75	10.7
10	O	16	i	Postpartum 5 days			5	7.63	5.90	0.77	15.1
10B	O	19	i	Postpartum 5 days			6	6.82	5.25	0.77	11.0
27	O	17	i	Postpartum			1¾	6.90	5.39	0.78	16.4
27B	O	26	iv	Postpartum 8 days			8	8.06	6.30	0.78	9.7
28	O	22	ii	Postpartum			7	7.20	5.70	0.79	11.3
29	O	38	v	Postpartum, hypertension			6	7.15	5.70	0.80	13.3
29B	O	19	iii	Postpartum 6 days			8	7.85	6.50	0.82	10.2
29C	O	26	iii	Postpartum 1 day			6	6.33	5.19	0.86	14.3
Average										0.737	

CHART 5—Permeability Ratio Before and After Delivery, Average Before 70.1, Average After 73

Num ber	Race	Age	Par ity	Clinical or Postmortem Diagnosis	Albu min	Blood Pres sure	Blister Time in Hours	Serum Pro tein, per Cent	Blister Pro tein, per Cent	Ratio B/S	Ratio B/S Change
67	W	20	i	Antepartum Postpartum fourth day	—	140/78	6½ 6	7.85 6.98	5.37 4.89	0.68 0.70	+0.02
68	O	19	i	Antepartum Postpartum fifth day	—	120/80	?	7.52 6.77	5.20 4.68	0.69 0.69	None
69	W	36	v	Antepartum Postpartum fourth day		Normal	6½ 6	7.70 6.65	5.29 4.89	0.70 0.73	+0.03
70	O	18	i	Antepartum Postpartum fourth day	—	110/80	?	7.63 6.55	5.19 5.05	0.72 0.77	+0.05
71	W	27	i	Antepartum Postpartum fifth day	—	128/86	6½ 8	6.98 7.20	5.21 5.20	0.74 0.72	-0.02
72	O	17	i	Antepartum Postpartum fourth day		Normal	6¼ 8	6.55 6.55	5.00 5.09	0.76 0.77	+0.01
73	O	21	i	Antepartum Postpartum fifth day		Normal	?	7.85 6.22	5.70 4.89	0.76 0.78	+0.02
74	W	20	i	Term March 2 March 16, postpartum 24 hours		Normal	6	6.65	?	?	?
				April 2, puerperal infec- tion (endometritis, streptococcus hemoly- sis)	+		8	7.63	5.23	0.68	
75	W	35	i	Eight months pregnant, March 2 April 2, seventh day post partum (multiple fibroid)			7¼	8.49	5.69	0.67	+0.07
76	O	23	i	In labor 14 hours Postpartum 6 days			8 6	7.34 8.06	4.37 5.90	0.59 0.74	+0.15

The observed differences in permeability can perhaps be shown more clearly in chart 1

It will be observed that during labor the capillaries of the skin are less permeable, and that relatively more of the antepartum than postpartum cases are in the group of lowered permeability (59-69), above that the postpartum cases predominate. The pathologic cases predominate in the groups of greatest permeability.

	IN LABOR	TERM							NORMAL	PATHOLOGICAL
59-64	IN LABOR	TERM							7	0
	POSTPARTUM									
65-69		TERM							13	2
		POSTPARTUM-2	WITH HYPERTENSION AND NEPHRITIS							
70-74		TERM							40	1
75-79			TERM-1 WITH NEPHRITIS						24	2
			POSTPARTUM-1	POSTPARTUM	ECLAMPTIC					
80-86			TERM-1 WITH NEPHRITIS	HEMATEMESIS	THREATENED ABORTION				8	6
			POSTPARTUM-1	WITH NEPHRITIS	SEPSIS	PSYCHOSIS				

Chart 1—Permeability ratio by groups. black columns, cases in labor, white columns, cases at term, shaded columns, cases postpartum, and crossed columns, pathologic cases.

GROUP				IN LABOR OR TERM				
I 59-69		POSTPARTUM						
II 70-74				IN LABOR OR TERM				
					POSTPARTUM			
III 75-86				IN LABOR OR TERM				
					POSTPARTUM			

Chart 2—Permeability ratio in groups of cases classified as (1) low permeability, (2) normal permeability and (3) high permeability (pathologic cases excluded). White columns, in labor or term, black columns, postpartum.

In chart 2 the pathologic cases have been eliminated and only three groups used: 1, relatively lowered permeability; 2, normal permeability; 3, increased permeability.

In surveying the tables it is interesting to note that the cases of hypertension with nephritis are to be found at the extremes of the range of permeability. In table 1 the single case of nephritis with moderate hypertension has a ratio of 0.77.

In table 2, two of the impermeable cases give a history of repeated infectious diseases, while at the permeable end is found a case of nephritis (blood pressure, 165) and one of hematemesis.

In table 3 the least permeable is a patient with toxemia during pregnancy, at the permeable end of the scale, an eclamptic case and a case of psychosis

In table 4 one case of hypertension is found with a normal rate (72), the other two are at the opposite ends of the scale

The change in permeability in such a condition as psychosis naturally brings up the question whether the increase in permeability results in the activation of a latent cerebral condition (in the nature of a focal reaction) or whether the development of the psychosis and the change in permeability are both merely coincident alterations based on some fundamental and underlying factor not determined

We incline to the concept that we deal with a focal reaction. We find a similar condition in the development of an alcoholic psychosis. Long continued injury has here created an unstable cerebral condition and any disturbance associated with an increased vascular permeability (an infection, trauma, a nonspecific injection, an added alcoholic debauch) will initiate and make clinically manifest a disturbance in an area that has already been the seat of a subclinical pathologic alteration. We have developed the subject at some length elsewhere.<sup>6</sup>

Obviously, a similar relation pertains in relation to the tuberculous focus, the details of which we have already discussed in the article on menstruation

In comparing the results of the study of the disappearance time of intradermally injected salt solution<sup>7</sup> with alterations in the capillary permeability in the normal and toxic pregnancies, a certain relationship is to be observed. In eclampsia, for instance, the disappearance time is markedly shortened and the capillary permeability increased. The shortening of the disappearance time has been interpreted as due to an increased affinity of the tissues for water.

Runge and Kessler<sup>8</sup> found that at the commencement of pregnancy there is a rise of osmotic pressure of the plasma colloids, this gradually falls after the fourth month, rises again suddenly during labor and again falls during the early days of the puerperium. The protein concentration of the plasma shows parallel changes, while the specific viscosity varies inversely. In the group of cases studied before and after delivery (table 5) the protein concentration at term was 7.436 per cent (ten cases) and 6.959 after delivery.

#### CONCLUSIONS

The capillary permeability of the skin during pregnancy averages 70.5 (forty-seven cases). During labor the permeability is reduced and the blister time increased (sympathetic tonus of the skin).

<sup>6</sup> Petersen, W. F. *Am. Rev. Tuberc.* **5**:218 (May) 1921.

<sup>7</sup> Lash, A. F. *Surg. Gynec. Obst.* **43**:40 (July) 1926.

<sup>8</sup> Runge, H., and Kessler, R. *Arch. f. Gynak.* **127**, Sept. 9, 1925.

During the puerperium the average permeability is 73.6 (fifty-five cases)

Psychosis, hematemesis, threatened abortion, postpartum eclampsia and sepsis were associated with increased permeability. Hypertension and nephritis were either high or low in capillary permeability, except in one case.

# THE PERMEABILITY OF THE SKIN CAPILLARIES IN VARIOUS CLINICAL CONDITIONS\*

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In the preceding articles of this series<sup>1</sup> we have discussed in detail some of the factors that underlie alterations in capillary permeability. We have emphasized that the endothelial cell of the capillary wall, quite apart from any adventitious muscular elements, is as every cell possessed of the property of changing the state of the cell membrane, becoming either more or less permeable as the case may be. This change is associated by coincident changes in the caliber of the capillary, for the cell membrane that is permeable limits a cell that is softer and less rigid, such cells when forming a tube (as a capillary) will be more readily pushed and stretched by any force on the inside of the tube. This leads to the dilation of the capillary. Such changes in the cell membrane depend (a) on the hydrogen ion concentration of the tissues and fluids concerned, this in turn involves (b) changes in equilibrium of the other ions, changes which become most apparent and which are best understood from the study of alterations in the calcium and potassium ratio. But such ionic rearrangement is only one of the factors with which we must deal, although perhaps the most primitive and, therefore, the most important. We must consider, second, the control by the hormones, some of which make the cells more permeable (parathyroid, sex gland, perhaps thyroid), others of which (suprarenals, pituitary) have the opposite effect. These, too, may act directly on the cells, but probably are greatly modified in their activity by the ionic equilibrium existing at the cell membrane. Finally, they depend on the actual autonomic nervous apparatus, which we commonly think of in terms of sympathetic and parasympathetic systems. The actual reaction elicited by such stimulation depends again on the ionic equilibrium of the cell at the time the impulse reaches it. For the capillary wall this third mechanism is, I believe, of less importance than the other two. The mechanism does, however, directly control the rate of flow to the capillary by its influence on the arterioles. Probably some sympathetic fibers actually control capillary caliber in a limited way in regions in which adventitial elements

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1 Petersen, W F, and Willis, D A. Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch Int Med* **38** 663 (Nov) 1926. Petersen, W F, and Milles, George. The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, *ibid* **38** 730 (Dec) 1926. Petersen, W F, and Lash, A F. Alterations in the Permeability of Skin During Pregnancy and Puerperium, this issue, p 12.

are well developed and constant in occurrence. We may with propriety speak of the vegetative control of the capillaries and to Kraus<sup>2</sup> and his school, as well as to the physiologist Ebbecke<sup>3</sup> we owe the greater part of the clarification that this particular field has undergone.

We should like to emphasize that while we speak of capillary permeability and have studied this particular phase of tissue activity in this series of articles, we recognize that the former is only an index of what is happening in the tissue in general.

We can trace much of the interest in the capillary and its importance in clinical phenomena to the work of Otfried Muller,<sup>4</sup> who has worked out many of the details of capillary microscopy.

From his laboratory, too, has come the suggestion that the ordinary cantharides blister might offer a useful method of approach to the problem of capillary, and tissue exchange and his associate Gansslen<sup>5</sup> was the first to publish work dealing with a study of clinical conditions. He gave particular attention to the blister time and to the relative concentration of sugar and nonprotein nitrogen in blood and blister fluid.

Gansslen applied six small plasters to the outer surface of the ankle and left these on for three, five, seven, nine, eleven and thirteen hours. The time of blister formation was then regarded as that time the plaster remained on the skin. His normal time was about twelve hours. This varied to some extent with different cantharides plasters employed and he also considered the possibility of seasonal variation. Gansslen did not make a comparative study of the amount of blister protein and serum protein, although Muller in his introduction mentions the probability that such a study might be of interest. Gansslen found a short blister time in the following conditions: vasoneuroses, urticaria, angioneurotic edema, dermatographia, urticaria factitia, hemorrhagic diatheses (one-fourth and one-fifth the normal blister time), and severe clinical conditions such as pernicious anemia, myelogenous leukemia, icterus, sepsis, endocrine disturbances—hyperthyroidism, Raynaud's disease with pituitary disturbance, following roentgen-ray castration of women, in one case of glomerulonephritis. He determined a prolonged blister time in hypothyroidism, myxedema, diabetes and in the chronic nephritides.

Among the factors that must be considered which will bring about such an alteration in blister time will be the relative status of the tonus of the skin vessels. Other conditions disregarded for the moment, prolonged blister time will represent cases with increased sympathetic tonus, short blister time those with hyperparasymphathetic tonus.

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2 Kraus, F., and Zondek, S. G. *Klin. Wchnschr.* **3** 707 (April 22) 1924.

3 Ebbecke, U. *Jahresb. d. ges. Physiol.*, 1922, p. 233, *Klin. Wchnschr.* **2** 88, 112, 1923.

4 Muller, Otfried. *Die Kapillaren der menschlichen Korperoberflache*, Stuttgart, 1922.

5 Ganssler, M. *Munchen med. Wchnschr.* **69** 263, 1922.

But in studying skin reactions we cannot assume that the relative tonus of the skin arterioles is a criterion for the tonus of the rest of the body. Muller and I<sup>6</sup> have demonstrated in a number of ways that there is a distinct antagonism between the status of the autonomic tonus of the peripheral as contrasted to the visceral regions. Consequently a sympathetic tonus of the skin vessels might be indicative of a parasympathetic status of the splanchnic area, and vice versa. We shall point out evidences of such conditions in the discussion of the clinical cases.

#### METHOD

The method that we have used differs from that of Gansslen in that we have put on only one plaster, and that on the flexor surface of the forearm just below the elbow. This area is free from hair, the skin is of uniform thickness in men and women and the small bandage needed is not inconvenient for the patient. The plaster was left on for six hours (unless the blister formed in the interim), was then removed and the area watched carefully for the first sign of blister formation. This was then taken as the blister time. The plaster was always put on at the same time in the morning (4 a. m.), and a uniform strength and supply of cantharides plaster used throughout in the experiments. Protein determination was made by the refractometer, the blister fluid being calculated from the "exudate scale" of the Reiss table, while the serum reading was calculated from the "serum" scale. The serum sample was always obtained from the ear lobe at the time the blister was punctured. The ratio  $\frac{\text{blister protein}}{\text{serum protein}}$  is used as our permeability index. In addition we have indicated for each patient  $\frac{\text{permeability index}}{\text{time of blister formation}}$  to make apparent the modification of the permeability by the time of blister formation. The latter ratio may, in a measure, be regarded as an index of the inflammatory response of the skin and capillaries. We have in addition studied the amount of glycytryptophan splitting enzyme present in blister and serum. This we have not tabulated for we have always found a much greater amount of enzyme in the blister fluid than in the serum. This has no necessary relation to the presence or absence of leukocytes in the blister fluid. The blister fluid should always be evacuated promptly when formed in sufficient amount. If left in the blister for any length of time the protein concentration begins to diminish, presumably because of proteolysis.

#### SKIN DISEASES

The skin cases, while small in number, offer several suggestive observations. The first case is that of a generalized dermatitis with a blister permeability of practically 100 per cent and prompt formation

<sup>6</sup> Muller, E. F., and Petersen, W. F. *Klin. Wchnschr.* **5**, no. 2, 1926.

TABLE 1—*Skin Cases*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albu mln	Nonprotein Nitro gen	Blood Pressure	Hemo globin	Red Blood Cells	Basal Metabolic Rate	Blister Time in Hours	Serum Protein, per Cent per Cent	Ratio B/S	R/T	
27	♂	W	64	(1) Generalized dermatitis exfoliativa (fatal) (2) Same, 3 weeks later			132/ 8				2	5.00	4.90	0.98	49.0
37	♂	W	23	Dermatitis herpetiformis (on arsenic)		40		90	4,200,000		1.30	4.70	4.65	0.98	65.0
122	♀	W	20	Dermatitis herpetiformis and early tuberculosis right apex		38					4	7.88	6.30	0.80	20.0
125	♀	W	21	Eczema		40				+16	5½	8.61	6.60	0.76	13.8
245	♂	W	59	Cellulitis of eye, diabetes, stricture posterior urethra, urticaria	++	58			5,400,000		5	8.49	6.18	0.72	20.6
				Three weeks later, on treatment with cal cium lactate, 15 grains three time a day, epinephrine chloride, 10 minims							10½	8.28	6.10	0.73	11.6
													4.89	0.59	5.6

\* In this column, ♂ indicates male, ♀, female

This would indicate that the skin capillaries are not in a condition of stasis, but of active hyperemia with the arterioles parasympathetically oriented

When we produce an active skin hyperemia (by means of ultraviolet irradiation) and wait until we have actual stasis (fourth day) with the surface red, hot and tender, a plaster will not produce a blister for a considerable period of time after one has been produced on the adjacent normal skin. Presumably the capillaries may here be permeable, but the arterioles are sympathetically oriented and in spasm.

Of the two cases of dermatitis herpetiformis, the one on arsenic is more permeable and has a shorter blister time than the second case. We have previously studied the rôle of arsenic on the capillary permeability.<sup>7</sup>

The effect of calcium lactate and epinephrine is well illustrated in case 245. From a permeability of 0.73 and inflammatory index of 14.6, the ratio is changed to 0.59 and inflammatory index 5.6.

As many of the problems of skin diseases and capillary permeability have been discussed very fully by Pulay<sup>8</sup> we shall not enter into the subject here.

#### CARDIORENAL CASES

We have grouped the cardiac and renal cases together, but have made subgroupings as noted in table 2. A large number of these cases have been observed at the county hospital, and it was not always possible to follow the individual cases to compensation or death to determine whether the disturbance was wholly cardiac or primarily renal. In the first group (*a*) are cases in complete decompensation of undoubted cardiac origin. In the second group (*b*) are decompensated or partially decompensated cases, as well as some practically recovered, of probable cardiac origin.

It will be noted that the permeability is very high in those with complete decompensation while in the second group a number have a normal permeability. The latter are cases in which arteriosclerosis was noted in the diagnosis or indicated by the relatively high blood pressure (cases 167 and 171) or had very little evidence of decompensation at the time the blisters were made (cases 19 and 39).

In the third group (*c*) have been collected cases primarily renal, but decompensated. Here, too, the permeability is very high. In the fourth group (*d*) are cases primarily renal or arteriosclerotic, all with some degree of decompensation.

<sup>7</sup> Petersen, W. F., and Hughes, T. P. *J. Pharm. & Exper. Therap.* **27**: 411, 1926.

<sup>8</sup> Pulay, E. *Ekzem und Urtikaria*, Berlin, Urban and Schwarzenberg, 1925.

TABLE 2—Cardiovascular Cases<sup>a</sup>[illegible]



In the fifth group (*e*) are the cases of hypertension and nephritis without decompensation. These cases have a low permeability and a relatively long blister time. The general capillary changes in nephritis associated with increased blood pressure have been studied in various

TABLE 3—*Acute Infections*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Blood Pressure	Non-protein Nitrogen	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
<b>A</b>												
172	♂	C	37	Acute multiple arthritis	102/63		99.4	10	7.80	6.00	0.77	7.7
198	♂	C	30	Acute arthritis			101	6	7.52	5.50	0.78	13.0
148	♂	W	35	Arthritis	130/60		98	10	8.18	6.10	0.74	7.4
194	♂		45	Polyarthritis with mitral lesion			N	6	7.00	5.29	0.75	12.5
184	♂	W	30	Gonorrhea, arthritis				9½	7.63	5.29	0.69	7.2
Average											0.74	
<b>B</b>												
154	♂	C	42	Lobar pneumonia lower right with mitral regurgitation and arteriosclerosis			103	13	6.90	6.30	0.90	7.0
155	♂	W	36	Lobar pneumonia			100	12	8.28	6.70	0.80	6.6
156	♂	W	31	Lobar pneumonia	120/77		101.5	3½	7.40	6.20	0.83	23.7
107	♂	W	54	Lobar pneumonia Four days later	136/78	58	104	9	6.90	5.50	0.79	8.7
					136/78	37	N	13	6.90	5.29	0.75	5.7
153	♂	W	36	Lobar pneumonia with streptococcus infection of shoulder	130/78		100.6	8	7.20	5.40	0.75	9.3
Average											0.81	
158	♂	W	24	Lobar pneumonia (just after crisis)			97.2	12	7.80	6.65	0.85	7.0
199	♂	W	35	Convalescent pneumonia			N	8	7.41	5.50	0.74	9.2
157	♂	W	42	Convalescent pneumonia	120/40		N	13	6.33	4.69	0.74	5.7
170	♂	C	34	Convalescent pneumonia			99	7	8.28	5.50	0.66	9.4
Average											0.71	
<b>C</b>												
233	♀	C	19	After bronchitis immediately post-febrile (6 months pregnancy and mitral insufficiency)	102/60			6	6.66	5.49	0.82	13.6
214	♂	C	24	Immediately following defervescence, bronchitis	112/74			15	8.28	6.70	0.81	5.4
110	♂	W	24	Postfebrile, had chill and temperature of 102				7¼	7.55	6.10	0.80	11.0
Average											0.81	
<b>D</b>												
5	♂	W	20	Normal, before influenza			N	5	7.20	5.35	0.74	15.0
				During influenza			104	5½	6.84	5.60	0.82	15.0
238	♂	W	30	Severe cold	108/54		N	6½	8.50	6.70	0.79	12.1
217	♂	W	23	Cold, sinusitis		43	100	7	7.41	5.69	0.76	11.0
197	♂	W	25	Convalescent typhoid	120/40		N	6	8.40	5.80	0.70	11.6

ways during the last ten years and the significance in our concept of cardiorenal disease sufficiently emphasized so that the low degree of permeability here shown need not surprise us. That such low permeability in itself need not necessarily have a direct bearing on the

disease is obvious from the fact that many of our normal controls have an equally low rate

We have examined only one child with nephritis (case 264, recurrent glomerulonephritis, extracapillary type) in which the capillaries were quite permeable, but the blister time retarded

#### ACUTE INFECTIONS

In the group of acute infections (table 3) a number of deviations from the normal become apparent

If we examine first a group of relatively mild infections (arthritis), the average age is 35, the blister time eight and one-half hours, the permeability ratio 0.74

Five cases of lobar pneumonia during the course of the disease (average age, 38) had a blister time of nine hours (of these four had prolonged blister time and one a very short period) The permeability ratio was 0.81

Immediately after the crisis (one case) the ratio was still 0.85 and the blister time still long (twelve hours)

During convalescence (four cases, average age, 41) the blister time was ten hours, the permeability ratio average 0.72

It is obvious that during lobar pneumonia the capillaries are more permeable than usual, that the increased permeability persists immediately after the crisis and then returns to normal. On the other hand the vessels have a predominatingly sympathetic tonus, with a resulting prolongation of the blister time which seems to persist even after the crisis

In three postfebrile cases examined on the morning of, or the day following, defervescence (bronchitis and one undetermined infection, cases 110, 204 and 233) the permeability was high, 0.81

In a student whose normal ratio was 0.74 the ratio was increased to 0.82 during influenza (temperature of 104 F)

#### TUBERCULOSIS

Exudative tuberculosis and advancing tuberculosis in general (table 4) is associated with an increased permeability (ratio from 0.75 to 0.85). Some of these cases have a prolongation of blister time (skin sympathetically oriented), but the majority are normal in this respect

Chronic tuberculosis is associated with a normal permeability of the capillaries and a normal blister time

Exudative cases on treatment, with absorption of fluid and lowering of febrile curve, have a lessened permeability

The relation of the type of tuberculosis to the relative autonomic tonus has been the subject of a number of recent papers, Guth,<sup>9</sup> in partic-

9 Guth, E. Beitr. z. Klin. d. Tuberk. 60:39, 1925

TABLE 4—*Tuberculosis*

Case No.	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albu- min	Casts	Phenolsulphon			Blood Pres- sure	Hemo- globin	Red Blood Cells	Tem- pera- ture	To	Blister Time in Hours	Serum Blister			
							Non protein	cin, Nitro gen	per Cent thal							Pro- tein, per Cent	Pro- tein, per Cent	Ratio B/S	R/T
249	♂	O	10	(1) Tuberculous peritonitis, six months duration (2) Tuberculous peritonitis (on treatment, temperature 99.100, fluid absorbing) Tuberculous peritonitis (mild)							45	3,500,000	To 103	8	7.98	7.00	0.87	11.0	
250	♂	O	6												12	8.92	4.72	0.53	4.4
225	♂	W	14	Tuberculous adenitis (pathologic report little tendency toward fibrous induration) Early tuberculous of hip (roent gen ray examination negative)							100	80	5,000,000	To 100	5	8.28	6.80	0.82	16.4
222	♀	W	6½											100 occasionally	4½	8.06	6.50	0.80	18.8
66	♂	W	14	Potts, psoas abscess, tubercu- losis of axillary glands Repeated 2 months later						104/74				101	6	7.85	6.10	0.78	13.0
205	♂	W	8	Tuberculous arthritis (?) (roent- gen ray examination pulmo- nary tuberculous probable) Pleurisy and effusion	++	++		43	92	128/85			5,000,000	To 100	5½ 5	7.20 8.28	5.50 6.80	0.76 0.82	13.8 16.4
121	♂	W	37												7	7.20	6.15	0.85	12.1
35	♂	O	20	Tuberculous peritonitis and pleural effusion (2) One week later on treatment (3) Five weeks later exudate all absorbed	+	++		38			60		6,000,000		6½ 5½ 6	7.97 7.63 8.92	6.48 5.49 6.70	0.82 0.73 0.75	12.6 13.2 12.5
	♂	W	15	Tuberculous of right upper lobe, active (with nephritis)			46	60	+	130/70	75		4,150,000	N	9½	7.12	5.80	0.81	8.5

[illegible]

TABLE 5—Gastric and Duodenal Ulcer

[illegible]

TABLE 6--*Carcinoma*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Blood Pressure	Phenolsulphon-		Hemo- globin	Blister Time Hours	Serum Protein, Protein, per Cent	Blister Protein, Protein, per Cent	Ratio B/S	R/T
								Non- protein Nitro- gen	tempera- ture						
A															
94	♀	W	47	Carcinoma of breast.	+	—	178/110		Normal		9	7.40	4.37	0.59	6.5
98	♀	W	49	Myxoma of abdominal wall trace	Trace	—	104/72	36	Normal		18	8.18	4.89	0.60	3.3
28	♂	W	66	Carcinoma of gallbladder, arteriosclerosis and arterio-sclerotic kidney	—	—		36			9	5.68	3.65	0.64	7.1
253	♂	W	69	Epithelioma on face	—	—	120/68	63	Normal		7	8.06	5.40	0.66	9.4
131	♂	W	55	Carcinoma of esophagus with gangrene of lung, spondylitis deformans, A S larger vessels of kidney	—	+	110/75	36			9	7.20	5.09	0.69	7.6
29	♂	W	34	Thymoma—with both kidneys infiltrated with metastatic tumor nodules							8½	7.08	4.89	0.69	8.1
187	♂	W	60	Carcinoma of esophagus							9¼	8.28	6.10	0.73	7.7
204	♂	W	47	Carcinoma of larynx—tracheotomy, bronchial pneumonia (kidneys normal on necropsy)						65	7½	6.98	5.82	0.83	11.0
Average														0.67	
B															
254	♂	W	54	Carcinoma of stomach				50	75	Normal	12	7.63	5.23	0.68	5.6
183	♂	W	50	Carcinoma of stomach ?							9½	6.49	4.47	0.69	7.2
60	♂	W	38	Carcinoma of pylorus	—	—	110/70	27		25	5	8.18	5.90	0.72	14.4
59	♂	W	53	Carcinoma of stomach	—	—		43			7	8.48	6.10	0.72	10.3
255	♂	W	68	Carcinoma of stomach	++	++	138/82		80	Normal	9	8.06	6.30	0.77	8.5
119	♀	W	48	Carcinoma of uterus, stricture of ureters, ascending pyelonephritis, beginning arteriosclerosis, hypostatic pneumonia	++	++	160/70	152		58	14	5.74	4.16	0.72	5.1
78	♂	W	53	Adenocarcinoma of stomach, metastases to liver, lymph glands, etc., kidney normal			108/72			20	6	5.90	4.47	0.75	12.5
Average														0.72	

TABLE 7 —*Goiter*

Case	Sex	Race	Age	Obitcal or Postmortem Diagnosis	Albu- min	Casts	Blood Pressure	Basal Metabolic Rate	Hemo- globin	Red Blood Cells	Non protein Nitrogen	Phenol sulphon phthalein, per Cent	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
218	♀	W	29	(1) Toxic adenoma (2) Five days after operation	Trace		150/90	+88					3	7.20	6.10	0.84	28.0
140	♂	W	37	Exophthalmic goiter	Trace		108/64	+64					4½	7.02	5.98	0.85	19.0
223	♀	O	40	(1) Exophthalmic goiter (2) Exophthalmic goiter (3) Exophthalmic goiter after operation			132/88	+65					5½	6.66	5.70	0.85	17.0
								+65					4½	7.00	6.00	0.85	16.0
													6	7.41	6.10	0.82	18.2
														7.20	5.60	0.79	13.1
7	♀	W	13	(1) Exophthalmic goiter with some pulmonary tubercu- losis (roentgen ray ex- amination)	Trace		128/70						2½	6.33	5.09	0.80	32.0
				(2) Exophthalmic goiter				+51					3	6.12	5.09	0.83	28.0
				(3) Exophthalmic goiter after operation				+18					2½	7.55	5.90	0.78	31.0
144	♂	W	25	Colloid goiter (had crisis after removal)			102/64						7½	7.85	6.16	0.78	10.4
15				Toxic adenoma				+62					5	7.63	5.74	0.75	15.0
15b	♀	W	42	Exophthalmic goiter 3 years, crisis 1 month before			140/80	+34					6	7.30	5.49	0.75	12.0
				weight loss, 35 pounds and													
207	♀	W	58	Exophthalmic goiter and arteriosclerosis			220/60	+68					6	7.52	5.59	0.74	12.0
31	♀	W	50	Toxic adenoma, myoearditis and arteriosclerosis	+	Ocea- sional	174/96	+50.70	70	6,000,000	38		7½	7.20	5.29	0.73	10.0
14	♀	W	45	Redi struma (no clinical symp- toms of exophthalmic goiter except weight loss, 10 pounds)				+42					5	8.28	6.04	0.73	14.6
M0	♀	W	32	Exophthalmic goiter	—	—	125/60	+75.100					5	7.73	5.48	0.70	14.0
20	♀	W	37	Obesity, hyperthyroidism, weight, 194 pounds, pulse 80	+			+40.50	70	4,600,000	43		1	8.70	6.10	0.70	17.5
A	♀	W	52	(1) Exophthalmic goiter dur- ing remission									4	7.32	4.98	0.68	17.0
15c	♂	W	24	(2) Blister on during operation	—	—	169/104	+25	80	5,700,000	32	42½	4	8.49	3.24	0.38	9.5
13	♀	W	25	Exophthalmic goiter 6 years Partial thyroidectomy, 1918, still nervous	—	Ocea- sional	125/70 118/80	+60 +11					4	7.95	5.30	0.66	16.5
													1	8.92	5.90	0.65	16.2

TABLE 8—*Miscellaneous Medical Cases*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Non-sulphon-protein phthalic, Nitrogen per Cent	Blood Pressure	Hemo-globin	Red Blood Cells	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
43	♂	C	25	Acute gastritis			55		70	4,000,000		13	7.00	5.90	0.84	6.4
143	♂	W	6	Hirschsprung's disease (megacolon)								4¾	6.77	5.70	0.84	17.0
220	♀	W	15	Impacted feces (megacolon?)	+			98/70	80	4,700,000	99	5	8.38	6.60	0.78	15.6
5	♀	W	26	Chronic appendix	—	—	49	130/70				6	8.70	5.70	0.65	11.0
147	♀	W	42	Cholecystitis	—	—		144/76				4	8.49	5.77	0.67	16.7
257	♀	W	51	Arthritis deformans	Trace	Few	46	118/78	78	4,250,000	100	8	8.92	7.20	0.80	10.0
203	♂	W	58	Arthritis deformans, hypertrophied prostate, lipoma of buttock	—	—	40	144/85				6	7.60	5.90	0.77	13.0
102	♂	W	51	Hypertrophic arthritis	—	—	36					6¼	7.30	5.50	0.75	12.0
16	♂	W	26	Asthma (2 years duration)	—	—		125/80				4	8.98	6.20	0.69	17.2
258	♀	W	29	Asthma (on epinephrine)	—	—						6	8.92	6.10	0.68	11.3
18	♂	W	25	Postanaphylactic shock (sore throat, nausea, vomiting, skin eruption, streptococcus infection?)			50	122/68				8	7.30	5.50	0.75	9.2

TABLE 9—Miscellaneous Medical Cases

Case	Sex	Race	Age	Chief or Postmortem Diagnosis	Albumin	Cysts	Non-Protein Nitrogen	Blood Pressure	Phenolsulphon phthalein, Cent	Hemo-globin	Red Blood Cells	Basal Metabolic Rate	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
26	♀	W	18	Obesity	—	—	38	115/70	—	87	4,800,000	+ 1		6	7.96	6.70	0.84	14.0
213	♀	C	36	Diabetes insipidus	—	++	25		90	75		Normal		4½	8.06	6.50	0.80	17.5
55	♀	W	40	Obesity	—	—	46	110/60	60	80	4,200,000	+ 6		5	8.49	6.50	0.78	15.6
259	♀	W	37	Obesity, hypertension	—	—	34	160/120	52	87	4,650,000	+12		6	7.28	5.49	0.75	12.5
42	♀	W	32	Obesity and diabetes insipidus			49	145/80						5	8.23	5.70	0.68	13.6
71	♂	W	65	Syphilitic cirrhosis with ascites, alcoholic neuritis, February 5 (2) March 6 (3) March 26	Trace	Occasional		120/80						8	5.35	3.55	0.66	8.2
56	♂	W	50	Syphilitic cirrhosis, chronic fibroid phthisis, edema of brain, kidney with little pathologic change except hyperemia, no ascites		Occasional	28							8	4.59	3.45	0.75	9.3
							6							6	5.17	3.86	0.74	12.3
														6	6.77	4.75	0.70	11.6
176	♂	W	61	Permeious anemia	—	Occasional	57	120/70	60	30-40	1,240,000		Normal	5½	7.00	5.60	0.80	14.5
219	♀	W	38	Permeious anemia, obesity	—	Occasional	36	180/90	50		1,640,000	+20	To 100	5½	7.41	5.60	0.75	13.6
265	♀	W	63	Paget's disease of bone	—	—	40	142/90		(Calcium 13.0)			Normal	7	7.20	6.40	0.88	12.5
				Paget's disease of bone, May 7						(Calcium 8.5)			Normal	8	6.49	4.61	0.71	8.8
32	♂	W	21	Hodgkin's disease	Trace	Occasional	34	104/65	45	80	5,000,000		Normal	6	8.23	6.50	0.78	13.0

ular, having studied the subject. We have shown in the group of normal persons that the group of low permeability contains many young men who have had more than the normal amount of pulmonary involvement, as determined by roentgen-ray examination and family history.

We believe it quite probable that the type of tuberculous reaction is determined by the relative tonus of the autonomic apparatus, of which the capillary permeability is in part an index. The permeability is of importance, moreover, because on its degree will directly depend, in a large measure, the type of reaction of the individual, i. e., whether exudative or proliferative.

In an article to be published elsewhere with Levinson we shall present a larger series of tuberculous cases and discuss the autonomic status in greater detail.

#### ULCER AND CARCINOMA

In five uncomplicated cases of ulcer of the stomach or duodenum (table 5) the permeability, as compared to the normals, is relatively high (average age, 43 years, average blister time, eight hours, permeability ratio, 74). It has frequently been suggested that in ulcer we deal with an autonomic alteration with a resulting spasm of the arterioles of the viscera. An increase in permeability such as we have here noted might be of interest in this connection.

The comparable cases of malignancy, seven in number (table 6), have a permeability ratio approximately the same, but the blister time is prolonged, so that the inflammatory index ratio is lower (carcinoma, 9, ulcer, 11).

The other cases of malignancy, with one exception, have a relatively low permeability and a prolonged blister time. Whether the difference is to be attributed to the age of the patients or to an increased sympathetic tonus of the skin we cannot at present determine. The lowering of the inflammatory index ratio would be in line with the general diminution of skin reactivity clinically observed in malignancy.

#### GOITER

Gansslen observed that some of his cases of hyperthyroidism had short blister time, while cases of hypothyroidism formed a blister only after long periods.<sup>5</sup>

In the small series here reported (table 7) it will be observed that the blister time is relatively short (parasympathetic orientation of the skin) but that the permeability of the capillaries varies from 0.66 to 0.85. This variation has no relation to the degree of activity of the symptoms either clinically or as determined by the basal metabolic rate.

Much has been written concerning the rôle of the autonomic nervous system in its relation to hyperthyroidism. Efforts have been made to fit the peculiar symptoms into a distinct picture of hypersympathetic

tonus, despite the fact that many of the phenomena are distinctly parasympathetic in type. It is obvious that the skin must be parasympathetically oriented, otherwise, with the greatly increased metabolic rate, the patient would have a high fever. We have previously shown that the skin-visceral orientation is usually opposite in character.<sup>6</sup> This being the case, we can understand that hyperthyroidism is associated with a low sugar tolerance. We have a similar condition in generalized dermatitis, where, with an increased parasympathetic tonus of the skin, the clinical picture usually shows a lowered sugar tolerance, occasionally with glycosuria. This is occasionally noted in other skin disease and may be sufficiently impressive that the patient is treated for diabetes, despite the fact that such cases have nothing wrong with the pancreatic secretion.

Among the exophthalmic cases, those with low permeability frequently, but not always, have a high blood pressure or other evidence of vasomotor change.

It is of interest to note that the lowest permeability noted in our whole series of clinical cases was in patient A, in whom a blister formed during the period of operation contained only 0.38 per cent of the protein present in the blood serum.

Usually the permeability and sometimes the rate of blister formation is reduced after thyroidectomy, but the patients have been kept for only a short period after operation, so that our observations have been necessarily limited.

#### MISCELLANEOUS MEDICAL CASES

Among the miscellaneous medical cases (tables 8 and 9) the cases of obesity (five in number) have a relatively high permeability and a short blister time, so that we can definitely put them into the group of cases with parasympathetic skins. In view of the fact that obesity is not infrequently observed as a postencephalitic sequel (as is also polyuria), this change is of interest for we find a similar condition in the postencephalitic parkinsonian syndrome.

The cirrhosis is of interest in that there is evident an increase in permeability as the case progresses.

A very high ratio was found in a case of Paget's disease of the bones. This was in an obese woman of 63, with typical roentgen-ray and histologic findings. The ratio was 0.88, with a blood calcium of 13 and a low sugar tolerance. Epinephrine injection was followed by a lowering of blood pressure. During her stay in the hospital the condition improved and the permeability ratio became lower (0.71) while the blood calcium also became much lower (8.6 mg). It may be recalled that Paget's disease of the bones has been frequently found associated with adenomas of the parathyroids.

TABLE 10—*Neurotic Diseases*

Case	Sex	Race	Age	Clinical Diagnosis	Albu- min	Blood Pressure	Non- protein Nitrogen (Caldium 12)	Phenol sulphon phthalen, per Cent	Temper- ature	Wass- ermann Reaction	Basal Metabolic Rate	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
226	♂	W	46	(1) Postinfluenzal parkinsonian disease (2) After malaria infection								6	7.20	6.30	0.87	14.5
21	♂	W	45	Postinfluenzal parkinsonian disease								5	6.45	5.20	0.80	16.0
77	♀	W	36	Postinfluenzal parkinsonian disease								10	8.28	6.30	0.76	7.6
243	♀	W	32	Postinfluenzal corpora striata lesion		110/80	36	73			+24	4	7.34	5.69	0.77	19.0
169	♂	W	63	Delirium tremens					100			4½	7.63	6.00	0.78	17.3
118	♂	W	16	Paresis						+++		4½	7.50	6.30	0.84	10.0
72	♂	W	56	Paresis?						Spl		9½	7.30	5.50	0.75	7.9
57	♂	W	28	Corpora striata, syphilis?						Spl		7	8.28	6.10	0.74	10.5
135	♂	W	41	Tubercles						+++		5	7.85	5.70	0.72	14.4
11	♀	W	19	Epilepsy since 12 years of age			31					6	8.18	5.90	0.72	12.0
92	♀	W	34	Epilepsy since 18 years of age, burn of arm 10 days before							+20	9	8.06	5.29	0.65	7.0
36	♀	W	19	Epilepsy since 10 years of age, burn of hand 2 weeks ago	++		46					6	8.70	4.68	0.54	9.0
139	♂	W	16	Little's disease with mental defect					Normal			5	8.01	6.60	0.82	16.4
235	♂	W	16	(1) Juvenile paresis (2) After malaria (10 days later)	Trace							10	7.74	6.20	0.80	8.0
97	♂	W	11	Acromegaly, idiocy					Spl *			6½	6.43	5.69	0.79	12.1
58	♀	C	6	Juvenile paresis								5½	8.39	6.46	0.77	14.0
12	♂	W	9	Traumatic epilepsy			36					5	7.20	5.30	0.73	14.6

An acute gastritis patient had a high permeability with a sympathetic skin tonus (internal organs parasympathetic)

The cases of arthritis deformans were all relatively permeable. Clinically, we realize that arthritis deformans represents something much more profound than merely an expression of joint and bone change. Observations of such capillary changes would confirm the notion that we deal with a far reaching alteration of the metabolism.

#### NERVOUS DISEASES

In the group of nervous diseases (table 10), of which we have a few at the present time, the postencephalitic parkinsonian syndromes are of most interest. That a great variety of autonomic disturbances become manifest during encephalitis and postencephalitis is obvious, and indeed the skin changes may be of such a degree that actual blister formation may take place. The two most marked cases (cases 226 and 21) had a high permeability, both associated with a relatively high blood calcium. In a third case in which the acute phase had been passed some years before, the permeability was much lower (case 77).

In a single case of delirium tremens the patient had a high permeability and short blister time. Of two adult parietic patients, one had a high permeability, the other was at the upper margin of the normal (0.75). In both, the skin was sympathetically oriented.

During menstruation a distinct increase in permeability was observed in a case of epilepsy.

The readings were as follows:

Menstruating	{ January 14,	Ratio $\pm$ 0.72	R/T = 12.0
	{ March 5	Ratio = 0.83	R/T = 18.3
	{ March 9	Ratio = 0.79	R/T = 13.0

Differences exist also in the capillaries of paralyzed extremities, as illustrated in a case of multiple sclerosis. The patient was aged 32, had paralysis of the right side for seven years and atrophy. The ratio in the left arm was 80, in the right arm, 90.

A second case, a small spinal cord cyst, showed no differences in permeability or blister time. This case had sensory but little motor change.

#### SURGICAL AND OPHTHALMOLOGIC CASES

Among the surgical cases examined, those with pathologic conditions in the kidney (table 11) have a low permeability, with the exception of one patient on hexamine. Many of the other patients examined shortly after some operative procedure had a high permeability, as will be seen from the table.

This increase in permeability is evident in ophthalmologic cases (table 12), usually associated with considerable pain. This may be

TABLE 11—Miscellaneous Surgical Cases

Case	Sex	Race	Age	Clinical Diagnosis	Albu- min	Cysts	Blood	Non protein Nitro- gen	Blood Pressure	Temper- ature	Wiss- mann	Leuko- cytes	Blister Time in Hours	Scum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
123	♂	W	35	Kidney stone (blister on du- ring operation)	+		+		132/90				7	6.98	4.00	0.57	8.1
122	♂	O	27	Stenosis of ureters	+		+	38	125/80				12	5.63	4.89	0.64	5.3
122	♂	O	77	Following prostatectomy 3 weeks previously (now on hexamine)	+	Oc- casion- al		50	128/84		++		20	7.41	5.90	0.80	4.0
76	♂	W	48	Stricture of urethra	Trace		—		130/86	To 99			5½	7.58	5.25	0.69	12.5
177	♂	W	7	Mastoid, chronic (not oper- ated on)	—								5	8.28	6.81	0.82	16.4
65	♂	W	33	Varicose veins, operated on 4 days previously					122/90				7	6.98	5.70	0.81	11.5
234	♂	W	39	Ulcer of rectum (tuberculo- sis?), cauterized 2 days previously, much pain				49	104/80				6½	7.20	5.69	0.79	12.1
208	♀	W	38	Hemorrhoids and appendix, operated on 4 days previ- ously									7	6.77	5.94	0.78	11.0
63	♂	W	48	Hernia, operated on 2 days before					134/90				5½	7.63	6.00	0.78	14.1
80	♀	W	17½	Appendix removed 2 days previously (sclerosis of mucosa)					116/68			11,150	5½	8.33	6.50	0.78	14.1
99	♂	W	6	Osteomyelitis, clavis and femur opened 2 weeks previously						To 100			5½	8.65	6.60	0.76	14.0
70	♀	W	32	Abscess of ilium (not oper- ated on)						To 100		15,000	7	9.35	7.11	0.76	11.0
62	♂	W	30	Rectal abscess 4 days after patient was operated on									6	7.63	5.70	0.74	12.0
82	♀	W	43	Abdominal hernia 2 weeks after operation									5½	7.63	5.78	0.74	13.5
101	♂	W	31	Postcholecystectomy 6 days after operation				49	108/80				5½	6.76	4.59	0.68	12.3

due to a more or less direct stimulation of the vagus as a reflex. In the table we have separated the juvenile cases from the adults because of their normal difference in permeability. It is nevertheless apparent that both groups have a relatively high rate, but that the rate of blister formation is not increased so that the inflammatory index ratio is rela-

TABLE 12—*Ophthalmologic Cases*

Case	Sex	Race	Age	Clinical Diagnosis	Albu- min	Blood Pres- sure	Non protein Nitro- gen	Blister Time in Hours	Serum Pro- tein, per Cent	Blister Pro- tein, per Cent	Ratio B/S	R/T
215	♂	W	8	24 hours after operation for strabismus				4	7.20	6.40	0.88	22.0
241	♀	W	13	24 hours after operation for strabismus				3½	8.39	7.11	0.84	24.0
116	♀	W	13	Left phlyete- nular keratitis				5½	7.85	6.60	0.84	15.0
120	♀	W	12	24 hours after operation for strabismus				7	8.07	6.80	0.84	12.0
227	♀	W	8	24 hours after operation for strabismus				6½	7.85	6.10	0.79	12.1
229	♂	W	12	24 hours after needling congeni- tal cataract				5½	8.40	6.50	0.76	13.8
130	♀	W	13	Congenital cat- aract				6	8.40	5.37	0.64	10.6
Average											0.80	
54	♀	W	64	Postoperative iridocyclitis (on acetylsalicylic acid, amido pyrine and atropine)	+	220/90		8	7.04	5.70	0.80	10.0
133	♂	W	59	Orbital cellu- litis (tumor?)	+	180/80	69	8	8.50	6.77	0.80	10.0
79	♂	W	29	Bilateral uveitis				5	7.47	5.90	0.79	16.0
247	♂	W	65	24 hours follow- ing cataract extraction				8	7.63	5.90	0.77	9.6
228	♂	W	77	Ulcerative ker- atitis				7	8.28	6.50	0.77	11.0
174	♂	W	23	24 hours after needling for traumatic cataract				7½	7.00	5.40	0.77	10.0
260	♀	W	63	24 hours after extraction of senile cataract				9	8.71	5.49	0.63	7.0
24	♀	C	27	Iritis				7	9.13	6.60	0.72	10.0
Average											0.75	

tively low. Whether the relative susceptibility to surgical shock and to intoxication from the absorption of the lens protein bears some relation to the alteration in permeability seen in these cases we cannot state.

## COMMENT

It is evident from these studies that distinct differences exist in the degree of capillary permeability observed by the blister method and that differences in the relative tonus of the arterioles can be determined when we study the blister time.

Generally, as we might anticipate, increase in capillary permeability goes hand in hand with a reduction in the blister time (parasympathetic tonus), the most striking example occurring in the case of generalized dermatitis. Other skin conditions apparently have a similar orientation, even if not to the same degree. It holds true for some cases of exophthalmic goiter.

Conversely, in lowered permeability we find the longest blister time, as for instance in some of the cases of arteriosclerosis and hypertension and epilepsy. Presumably these are distinctly sympathetic as far as the skin is concerned, although Kylan<sup>10</sup> has demonstrated that as far as the reaction to epinephrine is concerned cases of essential hypertension react with a vagotonic blood pressure curve.

But the capillary permeability and the apparent tonus of the arterioles need not be parallel. In the arteriosclerotic case with decompensation we may find high permeability (to 0.90) with a prolonged blister time, i. e., spasm of the musculature continuing with a damaged or fatigued capillary endothelium. We find a similar condition in an acute infection, such as lobar pneumonia, we find such cases not infrequently in tuberculosis.

On the other hand, we find the exophthalmic patient presenting uniformly a short blister time (parasympathetic orientation of the arterioles) with a variable permeability. Frequently the latter is high (0.85), occasionally reduced. (During operation in one case the ratio was the lowest observed in this entire series.)

When we review the various clinical conditions, the small group of skin diseases illustrates that the capillaries of the skin as a whole are changed in such conditions as dermatitis herpetiformis and eczema, as well as those conditions described by Gansslen. This is quite in accord with the work of Muller,<sup>11</sup> who has studied the reaction of the capillaries by means of the peripheral leukocyte count, and the work of Pulay,<sup>8</sup> who has studied the biology of the skin reactions from the dermatologic point of view. Parasympathetic orientation of the skin is associated usually with sympathetic orientation of the viscera, i. e., lowered sugar tolerance.<sup>12</sup>

With cardiac decompensation the capillaries become quite permeable, and this is obviously to be regarded as one of the factors in the production of edema. But the orientation of the arterioles may be sympathetic, i. e., spastic, as, for instance, with decompensation of hypertension. In nephritis, likewise, the capillaries may be permeable but the arterioles

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10 Kylan, E. *Klin. Wchnschr.*, no. 26, 1924, p. 28.

11 Muller, E. F. *Involuntary Nervous System. An Important Factor in Body's Resistance*, *Arch. Int. Med.* **35**: 796 (June) 1925.

12 Pulay, E. *Stoffwechsel und Haut*, Berlin, Urban and Schwarzenberg, 1925.

spastic Kidney conditions associated with strictures (urethra, ureters) have a low capillary permeability

In general, we can state that some evidence of capillary injury (or fatigue) with increased permeability is apparent with albuminuria and occasional casts in the student group. These may show either a rapid or slow blister time and there is, as a rule, no striking change in the blood pressure. In an advanced case of recurrent glomerular nephritis (extra-capillary type) the permeability was high, the blister time retarded (blood pressure high). Chronic nephritis associated with hypertension means spastic arterioles but in addition a capillary wall with retarded exchange.

Acute infection is associated with increased permeability and relatively sympathetic skin tonus, which, with the increase in metabolic rate, plays its part in the retention of heat and the phenomenon of fever. The increase in permeability is seemingly a transient affair for it is apparent for only some twenty-four hours after defervescence. Meyer<sup>13</sup> has called attention to the general phenomenon of parasympathetic over-tonus during defervescence.

Chronic tuberculosis is associated with normal or diminished permeability and sympathetic orientation of skin arterioles. This plays a part in the relative lability of the temperature reaction of the tuberculous person. Presumably such an orientation (generally sympathetic) is of benefit to the tuberculous person because of the diminution of absorption that it entails. The advancing type of tuberculosis is associated with relatively high capillary permeability, although the skin arterioles may remain sympathetically oriented.

Ulcer of the stomach and duodenum was found associated with an increase in permeability. I do not wish to enter into a discussion of the rôle of the autonomic unbalance which has been described in connection with these conditions. The results would lend some support to such a concept as a factor in the etiology.

The same holds true for exophthalmic goiter. It is clinically known that the autonomic symptomatology and particularly the vasomotor phases of the disease may be quite dissociated from the activity of the process as measured by the metabolic rate or the general condition of the patient. Indeed, many of the vasomotor phenomena may remain apparent long after the basal metabolic rate has returned to normal following thyroidectomy. Our cases give evidence of similar character. Throughout all the cases the blister time is diminished, as has previously been found by Gansslen. The skin arterioles are distinctly parasympathetic in orientation, accounting in a general way for the afebrile course of the

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13 Meyer, H. H., and Meyer-Gottlieb. *Experimentelle Pharmakologie*, ed. 6, Berlin, Urban and Schwarzenberg.

disease despite its high metabolic rate. The permeability, however, is subject to great variation. Some cases are very permeable, others with equal activity have a normal or retarded rate. In general, the latter cases are those with higher blood pressure, but there are exceptions.

That the capillary permeability depends on the ionic equilibrium of the tissues is best illustrated in the case of Paget's disease, in which with high blood calcium (low tissue calcium) the permeability is increased and with low blood calcium (higher tissue calcium) the permeability is retarded. These studies will be taken up in detail in a later article. Similar conditions prevail in the nervous diseases studied. Particularly in the epileptic cases we find that the increased frequency of attacks in the young women studied was associated with increased permeability in the premenstrual and menstrual days.

Patients following surgical operations as well as ophthalmologic patients with considerable pain present an increase in permeability. We assume that this is in part to be ascribed to the anesthetic, in part to the resorption of tissue protein, and in part to a reflex effect (perhaps as an indirect metabolic effect in the sense of Hamburger's "humoral transmission of nerve impulses") from the sensory stimulation.

#### SUMMARY

Capillary permeability of the skin vessels and the relative autonomic tonus of the arterioles has been studied by means of the cantharides blister.

Maximum permeability and parasympathetic tonus are found in generalized dermatitis.

Decompensation is associated with increased permeability. When due to renal or arteriosclerotic changes, the skin tonus may remain sympathetic.

Glomerulonephritis is associated with increased permeability with sympathetic arteriole tonus.

Chronic nephritis (arteriosclerotic) is associated with diminished capillary permeability and sympathetic arteriole tonus.

Acute infections show increased permeability with normal or increased sympathetic tonus. The increase in permeability persists immediately after defervescence.

Chronic tuberculosis shows normal or diminished permeability with normal or increased sympathetic tonus, advancing tuberculosis, an increase in permeability. Improvement is coincident with a diminution of capillary permeability.

Ulcer of the stomach and intestine shows a relatively high permeability, carcinoma, a somewhat lower range. This may be due to differences in the age groups.

Exophthalmic goiter has a distinct parasympathetic arteriole tonus but the permeability may vary from high to low. The cases with low permeability are usually those with a high blood pressure. The degree of permeability bears no relation to the basal metabolic rate.

Paget's disease of the bones and arthritis deformans have an increase in permeability. The same holds true for postencephalitic parkinsonian syndromes and for obesity.

Following surgical operations the permeability is increased and a similar condition is found in ophthalmologic cases with or without operation. This may be due to the anesthesia, to the resorption of necrotic material, or to reflex effects from the pain associated with these conditions.

# TOLERANCE IN RESPECT TO THE MENINGOCEREBRAL MANIFESTATIONS OF ACUTE AND SUBACUTE LEAD POISONING

EXPERIMENTAL PRODUCTION \*

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Clinical studies of human lead poisoning, particularly those of a statistical nature, have from time to time resulted in the conclusion that some degree of tolerance to the manifestations of this condition may be acquired through prolonged exposure to lead. The possibility of such an acquisition and the fact of its occurrence have been just as vigorously denied from other sources. It is the purpose of this article to show by an experimental method that, with the animal species used and methods employed, there can be demonstrated a marked degree of tolerance to the meningocerebral manifestations of lead poisoning. Thus, in still another instance has a clinical belief developed through careful case observation and statistical analysis found verification, although somewhat tardily, through laboratory investigation.

Tanquerel des Planches<sup>1</sup> in discussing a tabular survey of cases of lead encephalopathy said, "This table proves, among other things, that the greater number of patients have been exposed only a short time to lead preparations." And again, "The habit of frequent exposure to lead preparations does not prevent their action, but probably lessens their effects." The last clause indicates a belief in some degree of tolerance, but a contrary opinion is expressed somewhat later in the same discussion in these words: "But let them be once affected with encephalopathy, then, after their cure, they will be more liable to contract this disease than before being attacked with it, if they return at once to their labors."

Modern statistics, properly corrected for other variable factors, seem not to support the contention of Tanquerel des Planches that the greater number of patients have been exposed only a short time to lead preparations. Newman, McConnell, Spencer and Phillips<sup>2</sup> found that

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<sup>1</sup> Abstract presented at the meeting of the Association of American Physicians, 1926

1 Tanquerel des Planches. Lead Diseases, translation by Dana, edition of 1850, p 271

2 Newman, B J, McConnell, W J, Spencer, O M, and Phillips, F W. Lead Poisoning in the Pottery Trades, Public Health Bulletin no 116, 1921, U S Public Health Service, Washington, D C, p 120

in the pottery trades the rate of plumbism increases with the years of exposure. For males exposed less than one year the rate of positive plumbism was found to be 11 per cent, from one to five years, 56 per cent, from five to ten years, 65 per cent, and more than ten years, 134 per cent. The average length of exposure of the male positive group was found to be seventeen years.

No one has stated more emphatically a belief in an acquired tolerance in clinical lead poisoning than have Legge and Goadby.<sup>3</sup> Their definite statements on this point are worth quoting in full.

The experience of all persons engaged in the routine examination of lead workers is that, although a worker may show signs of lead absorption as distinguished from definite lead poisoning during the earlier period of his employment, he later shows less and less signs of the influence of the poisonous substance, even a mild degree of definite poisoning in the early stages of work in a lead process does not seriously militate against this gradually acquired tolerance.

Such statistics as are available on this point show that an increased tolerance to the poisonous influence of lead is gradually acquired during periods of work, in that the number of attacks of poisoning diminish in frequency very considerably in relation to the number of years worked. The greatest number of cases occur in persons who have only worked a short time in lead.

In persons employed in lead trades some species of tolerance is generally developed, and if the functions of the body progress in the normal way the balance of intake and elimination are equal.

In many persons who have worked in lead for long periods, wasting does not progress beyond a certain point, and these persons may be regarded as having established a certain degree of immunity. Such persons are either immune from the commencement, or they have established a certain degree of tolerance toward the metal, the latter supposition is the more probable, as there is reason to think that several of them suffered from mild degrees of poisoning during the earlier years of their employment.

In the recent monograph by Aub, Fairhall, Minot and Reznikoff<sup>4</sup> there is no reference to immunity in lead poisoning other than to those long recognized differences in susceptibility which are, in part, of an individual nature and, in part, are dependent on race, sex and age. The possibility of an acquired tolerance is not considered. This is in accord with the toxicology of lead as usually taught. Sollman<sup>5</sup> states that there is no acquired tolerance to lead, but that the natural susceptibility varies greatly as concerns the time, severity and symptoms of poisoning. These variations he attributes to differences in personal and factory hygiene, absorption and excretion, general health and resistance, and to other unknown factors.

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3 Legge, T. M., and Goadby, K. W. *Lead Poisoning and Lead Absorption*, New York, Longmans, Green & Co., 1912, pp. 28, 29, 38 and 113.

4 Aub, H., Fairhall, L. T., Minot, A. S., and Reznikoff, P. *Lead Poisoning*, Baltimore, Williams & Wilkins Company, 1926.

5 Sollman, T. H. *A Manual of Pharmacology and Its Application to Therapeutics and Toxicology*, Philadelphia, W. B. Saunders Company, 1922, p. 938.

The importance of the establishment of the possibility of an acquired tolerance in lead poisoning reaches beyond this metal alone. It is improbable that a specific antitoxic substance such as is developed against bacterial toxins, snake venoms and vegetable toxalbumins of the type of abrin and ricin will be found to explain such an immunity, if it does exist. A protective mechanism based on lessened absorption, accelerated excretion, destruction by oxidation or reduction or the formation of less toxic compounds ought rather to be looked for. Perhaps living cells "learn" how to vary their metabolic processes in such a way that they are affected less deleteriously subsequently than in their first experience with the toxic substance. At any rate, if alterations in the structure or in the behavior of the animal body can be produced of such a nature as to render it relatively tolerant to certain manifestations of one heavy metal it is fair to assume that similar mechanisms can be called out for other poisons of the same general group. Clinical evidence of a fragmentary nature, indicating that this is true, ranges from the reputed arsenic tolerance of Styrian peasants to the recent observation of Young, Hill and Scott<sup>6</sup> that in the administration of mercurochrome-220 second and third injections equal in size to the first almost always produce less reaction and that not infrequently there is no reaction following a dose that produced a very severe reaction at first.

Experimental evidence for the production of tolerance to heavy metal poisoning, while not abundant, has appeared from time to time in the literature. Much of this is buried in protocols of experimental work bearing titles that give no clue to the fact that such important observations are included. Chittenden and Lambert,<sup>7</sup> however, as early as 1889 recognized the significance of the relative tolerance to uranium salts which they found to occur in a dog to which ascending doses were being administered. After a period during which no uranium was given, approximately ten times the original dose was necessary in order to produce the same evidences of intoxication. It is not clear that due allowance was made for lagging of the signs of poisoning behind the actual period of administration. West<sup>8</sup> was aware of this observation and, during experimental treatment of diabetes mellitus with uranium nitrate, found that with one of his patients it was necessary to give very much larger doses in order to get the same therapeutic effect as before,

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6 Young, H. H., Hill, J. H., and Scott, W. W. The Treatment of Infections and Infectious Diseases with Mercurochrome-220 Soluble, *Arch. Surg.* **10**: 813-924 (May) 1925.

7 Chittenden, R. H., and Lambert, A. Untersuchungen über die physiologische Wirkung der Uransalze, *Ztschr. f. Biol.* **25** 513-532, 1889.

8 West, S. Uranium Nitrate in Diabetes Mellitus, *Brit. M. J.* **2** 467-472, 1895.

if uranium-free intervals had elapsed. Later, Suzuki<sup>9</sup> made the interesting observation, based however, on meager evidence, that regenerated renal epithelium following uranium poisoning showed remarkably less susceptibility to a subsequent exposure to the same or a larger dose. This regional acquired immunity was further investigated by Gil y Gil,<sup>10</sup> who found that rabbits poisoned with uranium nitrate would survive many times the lethal dose if graduated doses separated by proper intervals were administered in series. He thus produced in seven animals varying degrees of tolerance to uranium nitrate administered subcutaneously and intravenously. Similar results were obtained with mercuric chloride. He believed the acquired immunity to reside in the renal parenchyma itself and that it was developed unequally in different segments of the glomerulotubular system so that one portion might still be susceptible after another had become relatively resistant.

As to the experimental production of tolerance in lead poisoning, a rather complete search of the literature gives no indication that this has been accomplished hitherto. Legge and Goadby<sup>11</sup> found that in certain dusting experiments the animals maintained a state of equilibrium and even a certain degree of tolerance to the effect of lead dust, in that their weights remained almost constant. When the lead content of the air was as low as 0.00001 Gm per liter, in more than one instance, after an initial diminution in weight, recovery of the lost weight took place. However, an increase in the quantity of lead dust present in the air immediately produced progressive loss in the body weight. There is no evidence that, under the conditions of the experiment, any important increase in resistance to lead was developed.

Reduced to its simplest terms the demonstration of experimentally produced tolerance to any poison consists of three steps. In the first place it is necessary to select some manifestation of the poison as an indicator of the degree of intoxication. Next, some quantitative expression of the dosage that normally produces this effect must be determined. Finally, it must be shown that under identical conditions of administration animals have gained the power of withstanding a considerably larger dosage without a corresponding appearance of the manifestation previously selected as an indicator.

The choice of the test manifestation is of the greatest importance. In experimental lead poisoning such indications of intoxication as loss of weight, palsy and the appearance of stippled cells in the blood lack the factor of definiteness which a good indicator of an "end reaction" should have. They are capable of appearing in such slight degrees that

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9 Suzuki, T. *Zur Morphologie der Nierensekretion*, Jena, 1912.

10 Gil y Gil, C. *Die Immunität im Nierenepithelgewebe*, Beitr. z. path. Anat. 72: 620-653, 1923-1924.

11 Legge and Goadby (footnote 3), pp. 31 and 83.

the presence or absence of the test sign becomes problematical. The lethal effect of the intoxication may, of course, be used as the indication of relative susceptibility and possesses the quality of sharp definition in the highest degree. But death of the animal in the second step of the proof means that tolerance is never demonstrated in the same animal in which the normal intoxicating dosage has been determined. The comparison under such circumstances has to be between the apparent resistance of particular animals and the known susceptibility of a group of animals of similar species, age, sex and weight. The proof of acquired tolerance is more convincing when it rests, at least in part, on the performance of the same animals before and after the acquisition of the greater resistance to the poison. For this reason lethal effect is not the best criterion that can be selected. It is desirable, also, that the test manifestation should be one that does not show too long a latent period for its development. If it does, uncertainty may exist as to which stage in an ascending scale of dosage was sufficient to produce it. For the same reason, conditions that are to any considerable degree dependent on a cumulative action of the poison are not well suited to this purpose.

In the meningocerebral manifestations of experimental lead poisoning, particularly as exhibited by the guinea-pig, we have an indication of intoxication that is especially well adapted to the investigation of tolerance. If lead compounds be administered by mouth in suitable amounts practically all guinea-pigs within a short time develop characteristic convulsive seizures closely resembling those found in human lead meningo-encephalopathy. After showing increased excitement and a behavior interpretable as a state of apprehension, the animal passes suddenly into a violent clonic convulsion, rushing madly around its cage and throwing itself headlong against the walls or any object in its way. This lasts for a few seconds only. Then the animal drops motionless in an equally severe tonic phase. There is usually a slight degree of opisthotonos but every skeletal muscle is involved and respiration is suspended. After an interval varying from a few seconds to a minute or more the tonic contraction begins to pass off and soon the animal takes short gasping respirations and gradually recovers, although remaining dazed or lethargic, rarely actively delirious, for some time. Death may occur during the first, or in a subsequent, convulsion and seems to depend primarily on suspension of respiration. If the animal is taken up at once during the tonic phase and artificial respiration applied its life may be saved when it would otherwise die. So violent is the clonic phase that it will always be noted by an attendant in or near the animal room, facilitating an accurate record of the occurrence of convulsions. Even when the seizures come at night, record is still possible since, in the usual type of wire cage, the animals practically always receive

abrasions on the nose from dashing against the walls. In male animals there is a discharge of semen during the convulsion. This coagulates quickly and remains for some time as a plug in the penile sheath. Inspection of such animals in the morning permits accurate tabulation of convulsions occurring during the night. Because of this special advantage male animals chiefly have been used for the experimental series here reported.

From this brief description of the characteristic epileptiform convulsion of lead meningo-encephalopathy in the guinea-pig it will be seen that this reaction lends itself very well for use as an indicator in statistical study. It either does or does not occur. Examined critically, it has only one disadvantage and that, fortunately, is not of serious importance when many animals are being used. This is the fact that when an animal is severely poisoned with lead a convulsion may be precipitated by excitement or by a sudden noise, such as the banging of the cover of the cage. If one of four animals in a cage has a convulsion one or two of the others may develop convulsions while the first is dashing about in its clonic phase. It might at first thought appear that this would introduce a double error, causing false positives in animals that would not spontaneously develop convulsions and leaving in the negative group equally, or even more severely, poisoned animals that happened to have escaped any inciting factor. It seems certain, however, that when convulsions are precipitated in this manner they occur only somewhat prematurely and that practically all such animals would exhibit convulsions later anyway. Since many animals having convulsions do not die, it is possible to test for tolerance in respect to this manifestation on animals known to have been previously susceptible to a certain amount of lead. In any investigation of tolerance, this constitutes an important advantage.

In the various series of animals utilized in this report, lead, in the form of commercial white lead or of chemically pure lead carbonate, was administered by mouth in gelatin capsules. The amount given was obtained by taking the average weight of the tared contents of all the capsules in a given batch. Greater accuracy was obtained by using a diluent and filling the capsules completely with the mixture. For this purpose linseed oil and cornstarch were used with commercial white lead, and cornstarch alone with lead carbonate. The animals were kept on a standard diet that has proved adequate for many years in a colony of guinea-pigs maintained as controls and for breeding purposes. The small range of dosage used in the reported series (from 0.126 to 0.171 Gm. of commercial white lead and 0.155 Gm. of chemically pure lead carbonate) was made possible through previous experience with this method of administration and was known to be an amount that would produce convulsions in untreated animals after about four

consecutive daily doses No effort was made to determine the amount of lead absorbed This could be found approximately by taking the difference between the amount administered and that recovered from all of the feces of each animal, collected separately and uncontaminated with urine It was felt that the information thus obtained, while of the greatest importance in investigating the mechanism of tolerance, was not essential to a demonstration of the fact of the acquisition of tolerance The reason for this will be considered in the discussion of the results Of greater importance is the length of time during which fresh supplies of lead are made available for absorption, for dosage depends not only on the amount given but also on the rate and duration of administration These factors as influencing the acquisition of tolerance must be the subject of a later article In all series of animals used in this report one capsule was given each day during the period of lead intake

TABLE 1—*Determination of Lethal Dosage of Lead Carbonate*

Guinea Pig	1	2	3	4	5	6	7	8	9	10	11	12	13	14
X149	250 Pb	Pb	Pb										†	
X150	675 Pb	Pb	Pb +		+					†				
X151	665 Pb	Pb	Pb			+								
X152	585 Pb	Pb	Pb	+	+			+						
X153	600 Pb	Pb	Pb	Pb	Pb		+							
X154	685 Pb	Pb	Pb	Pb	Pb		+		†					
X155	535 Pb	Pb	Pb	Pb	Pb			+				†		
X156	675 Pb	Pb	Pb	Pb	Pb			+		†				

In this and the following tables, Pb indicates a single administration of lead, in this case 0.155 Gm. of chemically pure carbonate of lead, the plus sign, the occurrence of convulsions, the dagger, death of the animal.

This table illustrates the method of determining the convulsion producing and lethal dosage of lead carbonate. Three doses of 0.155 Gm. each given on consecutive days produce convulsions and may kill. Five such doses not only produce convulsions but are always lethal.

The amount of lead carbonate, administered as described, capable of producing convulsions in animals with no previous exposure to lead is shown in the tabulated protocols given here. For instance, in table 1 is shown a test series for the determination of the convulsion producing and lethal dosage of lead carbonate. The column at the left designates individual guinea-pigs by number, the figures across the top, days of the experiment. The initial weight of each animal is given in grams for the first day. Pb indicates a single administration of lead, in this case

0.155 Gm of chemically pure carbonate of lead, the +, the occurrence of convulsions, the †, death of the animal Guinea-pig X149, dying on the thirteenth day, was never seen to have a convulsion, although its death makes it practically certain that its reaction was not exceptional in this respect. If we make this assumption, it will be seen that three consecutive daily doses of this size will produce convulsions and may kill while five such doses produce convulsions and cause death of all animals so treated. These results, with others not tabulated, may be summarized as in table 2, in each instance the number of doses given means the number of consecutive doses administered.

TABLE 2—*Effect of Commercial White Lead and Chemically Pure Lead Carbonate (Mallinckrodt)*

Commercial White Lead		
4 doses of 0.126 Gm	produced convulsions in	12 of 12 animals
2 doses of 0.162 Gm	produced convulsions in	2 of 4 animals
1 dose of 0.171 Gm	produced convulsions in	1 of 4 animals
2 doses of 0.171 Gm	produced convulsions in	1 of 1 animals
3 doses of 0.171 Gm	produced convulsions in	3 of 3 animals
4 doses of 0.171 Gm	produced convulsions in	2 of 2 animals
Chemically Pure Lead Carbonate (Mallinckrodt)		
3 doses of 0.155 Gm	produced convulsions in	3 of 4 animals
4 doses of 0.155 Gm	produced convulsions in	2 of 2 animals
5 doses of 0.155 Gm	produced convulsions in	6 of 6 animals

It will be noted that within the range of size of dose used, four consecutive daily doses produced convulsions in every instance and three consecutive daily doses in every case but one. As to the lethal effect, all untreated animals receiving five consecutive daily doses of either form of lead and ten out of sixteen receiving four consecutive daily doses died. Under these conditions of administration, then, it may be stated in a general way that all animals receiving four or more consecutive doses develop convulsions and that those receiving five or more doses die. This establishes the quantitative relation subsequently made use of in determining whether or not there has been a gain in tolerance.

In the course of another group of experiments in which it was necessary to obtain material for histologic examination of the central nervous system of animals dying in convulsions after the oral administration of lead,<sup>12</sup> it was found that those guinea-pigs which survived convulsions required a longer period of lead administration in order to induce this manifestation a second time. This observation became the basis for the series of experiments reported here. It was soon found that the most important factor, apparently, leading to relative tolerance in respect to this evidence of lead poisoning was the interpolation of recovery periods between the periods of lead administration. In table 3

<sup>12</sup> Weller, C. V., and Christensen, A. D. The Cerebrospinal Fluid in Lead Poisoning, *Arch Neurol & Psychiat* 14 327-345 (Sept.) 1925.

TABLE 3—*Induced Tolerance for Commercial White Lead*

Guinea Pig	1	2	3	4	11	12	13	14	15	16	35	36	37	38	39	40	41	42	43	44	45	46	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83
X119	330 Pb Pb Pb Pb				280 Pb Pb Pb Pb				283 Pb Pb Pb Pb	295 Pb Pb Pb Pb											298 Pb Pb Pb Pb	300 Pb Pb Pb Pb																347 Pb Pb Pb Pb
X120	460 Pb Pb Pb Pb																																					
X121	470 Pb Pb Pb Pb																																					
X122	320 Pb Pb Pb Pb																																					
X123	370 Pb Pb Pb Pb																																					
X124	360 Pb Pb Pb Pb				315 Pb Pb Pb Pb																																	
X125	370 Pb Pb Pb Pb				330 Pb Pb Pb Pb				327 Pb Pb Pb Pb	362 Pb Pb Pb Pb											310 Pb Pb Pb Pb		320 Pb Pb Pb Pb															277 Pb Pb Pb Pb
X126	310 Pb Pb Pb Pb				300 Pb Pb Pb Pb				325 Pb Pb Pb Pb	362 Pb Pb Pb Pb											337 Pb Pb Pb Pb		345 Pb Pb Pb Pb															288 Pb Pb Pb Pb

Pb = 0.126 Gm of commercial white lead (0.162 Gm after seventy eighth day)  
 Three out of eight animals were able to withstand sixteen consecutive doses of white lead, four times the convulsion producing dose and three times the lethal dose, without either convulsions or death resulting, although all three of these animals had shown convulsions following the first series of but four similar doses

is shown a condensed protocol illustrative of the method used. This table is constructed on the same plan as was table 1 except that symbols indicating convulsions and death do not appear on it. All of the eight guinea-pigs in this group had convulsions following the first period of lead administration. The day of death and weight in grams at death of the five that died appear in their proper positions. The resting intervals between successive periods of lead administration are shown by the gaps in the series of consecutively numbered days of the experiment in the upper line of the table. It will be seen that four of the eight animals in this particular series died following the first period of lead administration, which consisted of four doses. A rest period of six days intervened and the survivors were then given six similar consecutive doses. One was lost during this period. After a rest period of eighteen days, the three survivors withstood twelve consecutive daily doses without convulsions, and finally after a rest period of twenty-one

TABLE 4—*Induced Tolerance for White Lead*

X119	Pb 4	[6]	Pb 6	[18]	Pb 12	[21]	Pb 16
X120	Pb 4	Died					
X121	Pb 4	Died					
X122	Pb 4	Died					
X123	Pb 4	Died					
X124	Pb 4	[6]	Pb 5	Died			
X125	Pb 4	[6]	Pb 6	[18]	Pb 12	[21]	Pb 16
X126	Pb 4	[6]	Pb 6	[18]	Pb 12	[21]	Pb 16

Pb dosage per day = 0.126 Gm. of commercial white lead by mouth (0.162 Gm. in final series)

This table shows in condensed form the same data embodied in table 3. The unbracketed numbers indicate consecutive days of lead administration, the bracketed numbers, the duration in days of the recovery periods between succeeding periods of lead administration.

days they survived sixteen doses, four times the amount that produces convulsions in all untreated animals and death in one half of them. In this instance each daily dose was 0.126 Gm. of commercial white lead up to the seventy-eighth day of the experiment and 0.162 Gm. of commercial white lead thereafter. Thus, six doses of the larger size were given toward the end of the final sixteen dose series. Five consecutive doses of this magnitude always kill untreated guinea-pigs. The essential data of this experiment are condensed and indicated more clearly in table 4. The history of each animal as to "leading" is shown, the number following each Pb indicating consecutive days of lead administration and the numbers in square brackets, the interpolated free periods.

Animals in which there has been induced a relative tolerance of the type shown by the three survivors of the group just described may henceforth be used as controls in groups of untreated animals with most interesting results. In table 5, for instance, guinea-pig X126 from an earlier series was "lead" with seven previously untreated animals

TABLE 5—Experimentally Induced Tolerance to the Meningoencephal Manifestations of Poisoning from Commercial White Lead

[illegible]

Pb = 0.171 Gm of commercial white lead  
The previously treated animal, guinea pig X<sup>120</sup>, is utilized as a control in the group

Although no convulsions resulted in this animal from four, and shortly thereafter from twelve, consecutive doses, the untreated animals showed convulsions from an initial series of three and four doses, the later causing death. In one instance a convulsion followed a single administration. The death of one animal (guinea-pig X141) after the third series of three doses and of another (guinea-pig X138) after a fourth series of six doses is interpreted as indicating that the free periods were too short. Only guinea-pig X136, X139 and X140 in this group acquired a significant degree of tolerance. The gain in weight of the control animal contrasts with the general loss of weight of those receiving lead for the first time, but in the latter there is a definite tendency for the lost weight to be regained if some degree of tolerance is acquired. This is true particularly of guinea-pig X139. One purpose in arranging the dosage for this group was to investigate the rôle played by the convulsions themselves. It seemed possible that certain changes might be induced by the violent convulsions of such a nature as to render the animal less susceptible to future convulsive seizures. By giving only one capsule in the first series and reaching the convulsion producing level of four doses by increments of one only, two animals from this group, guinea-pigs X139 and X140, were made to acquire a high degree of tolerance without at any time having suffered from convulsions. Such evidence as this shows that convulsions are not themselves essential to the acquisition of tolerance to the convulsive manifestations of lead meningo-encephalopathy.

An even more striking test of the acquisition of tolerance can be obtained by using untreated animals as controls in groups made up of those which have been prepared by a graded series of increasing periods of "leading." Such a grouping is shown in table 6. Six guinea-pigs previously treated with lead compounds were combined with two untreated animals and all were given five consecutive daily doses of 0.155 Gm. of lead carbonate. This amount, as has been previously shown, invariably induces a fatal series of convulsions in untreated animals. The six previously exposed to lead had no convulsions and none died. The preparatory administration of lead is shown in the right hand column. This information for guinea-pig X145, for instance, is to be read as follows: Sixty-four capsules of white lead over a period of eight months, a free period of one year, six consecutive daily doses, a rest period of thirty-seven days, ten consecutive daily doses and a final rest period of sixty-two days before starting the period of lead administration detailed in this table. The two untreated animals developed convulsions and died, as was expected. It will be noted that the six animals showing tolerance, as a group, suffered no significant loss of weight.

There is some evidence indicating that, whatever the mechanism of this type of tolerance may be, it persists and is still operative after a long time. In table 7 are condensed the protocols of four guinea-pigs that had received many small doses of white lead over a period of eight

TABLE 6—*Acquired Tolerance for Lead*

Guinea-Pig	1	2	3	4	5	6	7	8	9	10	11	12	13	Previous "Leading"
X145	760 Pb	Pb	Pb	Pb	Pb								760 Pb	64 in 8 months [1 year] Pb 6 [37] Pb 10 [62]
X146	730 Pb	Pb	Pb	Pb	Pb								680 Pb	3 [10] Pb 6 [54]
X148	710 Pb	Pb	Pb	Pb	Pb								700 Pb	2 [10] Pb 4 [56]
X151	770 Pb	Pb	Pb	Pb	Pb								770 Pb	3 [22] Pb 5 [34]
X152	670 Pb	Pb	Pb	Pb	Pb								725 Pb	3 [22] Pb 5 [34]
X157	770 Pb	Pb	Pb	Pb	Pb								775 Pb	4 [35]
X159	850 Pb	Pb	Pb	Pb	Pb									None
X160	800 Pb	Pb	Pb	Pb	Pb								†	None
								+						

Pb = 0.155 Gm of chemically pure lead carbonate (in previous "leading" various dosages). This table compares the response of six guinea pigs previously treated with lead with that of two untreated animals when all are given five 0.155 Gm doses of lead carbonate on consecutive days. The two controls developed convulsions and died. The six animals prepared by the previous administration of lead showed no convulsions and none of them died.

TABLE 7—*Persistence of Tolerance to the Meningococcal Manifestations of Lead Poisoning*

Guinea Pig	1	2	3	4	5	6	7	8	9	Previous "Leading"
X142	715 Pb	Pb	Pb	Pb	Pb	Pb			715	64 doses in 8 months, no lead for 1 year
X143	775 Pb	Pb	Pb	Pb	Pb	Pb			700	78 doses in 8 months, no lead for 1 year
X144	600 Pb	Pb	Pb	Pb	Pb	Pb			630	67 doses in 8 months, no lead for 1 year
X145	715 Pb	Pb	Pb	Pb	Pb	Pb			600	64 doses in 8 months, no lead for 1 year

Pb = 0.171 Gm of commercial white lead. No convulsions appeared in four guinea pigs which had received no lead for one year but which had been "leaded" before that period. Six consecutive doses of the size given here will cause convulsions and death in untreated animals. Although the record is continued for only nine days, this group was kept under close observation for one month after lead administration ceased and no convulsions occurred.

months in the course of another investigation. They were then put aside for one year. When treated, they withstood without convulsions six consecutive daily doses of 0.171 Gm of white lead, an amount always causing convulsions and death in untreated animals. If further investi-

TABLE 8—*Convulsions in 100 Per Cent of Group*

Guinea Pig	1	2	3	4	5	0	14	15	16	17	18	19	20	21	46	47	48	49	50	51	52	53	54	55	57	58	59	60
X127	220 Pb	Pb	Pb	Pb	Pb	+																						
X128	400 Pb	Pb	Pb	Pb	Pb	+																						
X129	225 Pb	Pb	Pb	Pb	Pb	+																						
X130	400 Pb	Pb	Pb	Pb	Pb	+	2.10	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	415 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	+	+

Pb = 0.126 Gm of white lead in first series  
Pb = 0.162 Gm of white lead in second and third series  
Such series demonstrate not only the absorption of lead by all the test animals, but also the fact that in our experience no guinea pigs have been found having such an intrinsic degree of tolerance that it convulsions cannot be induced in them

gations along this line, now under way, confirm this observation such a remarkable retention of acquired tolerance will in itself throw light on the mechanism involved

Certain objections to the conclusion that this series of experiments demonstrates the acquisition of tolerance are anticipated. The argument must be kept as simple as is possible. A particularly clear cut manifestation of lead poisoning has been selected, the dosage eliciting this in untreated animals determined and, by the interpolation of rest periods between gradual increments in dosage, treated animals have been given four times this amount without the appearance of the test sign. This fact, not tolerance for lead in general and not the mechanism concerned in its production, forms the subject of this report.

Are the results obtained due to failure to absorb lead from the gastro-intestinal tract? The dosage used produced convulsions in all untreated animals and most of those which finally exhibited tolerance had themselves suffered from convulsions during their earlier "leading." We have never found a guinea-pig that did not absorb lead in sufficient amount to produce convulsions if it had never had lead before. By using an initial series of doses of sufficient size every animal in a group may be made to show convulsions. This is illustrated by table 8. Since the borderline between the production of convulsions and death is very narrow there will not be many survivors to develop tolerance if this is done. In this instance a relative degree of tolerance was gained by the sole surviving animal which succumbed to a third series of twelve consecutive doses. If lead is absorbed less easily after the preparatory treatment than before, that is part of the mechanism by which tolerance is developed and, although of the greatest interest and importance, is not part of the demonstration of tolerance itself. That point must receive further investigation.

Are the results obtained due to a selective process, the susceptible animals dying and the more resistant ones remaining to be called tolerant? Since individual differences exist among laboratory animals as among human beings in respect to their susceptibility to lead this type of selection is bound to occur to some extent. It cannot explain the results reported here since no animal has been considered as having acquired a relative tolerance unless it has gained the power of withstanding a greater dosage than not only it, but also any other similar animal, could withstand before treatment. As is indicated by table 8, to which reference has just been made, intrinsic immunity of such a degree that convulsions cannot be induced apparently does not exist in the guinea-pig. Thus, the factor of selection through elimination by death is ruled out.

We believe that the results reported here constitute a demonstration of experimentally induced tolerance to lead poisoning in respect to the meningeocerebral manifestations as they occur in the guinea-pig.

# THE DETOXICATION OF PUTREFACTIVE PRODUCTS BY THE HUMAN BODY<sup>1</sup>

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The work of the many investigators on the relation of the liver to blood pressure, especially that of Major<sup>1</sup> and of James, Laughton and McCallum<sup>2</sup> is keeping before our minds the importance of the chemical functions of the liver. Besides these very interesting reactions there are also those of the detoxication of toxic organic compounds, either those naturally produced by bacterial decomposition of waste material in the body or those introduced into the organism in the course of experimental work. It is with the latter reactions that our laboratory has been chiefly interested during the last ten years,<sup>3</sup> in fact, the detoxication reaction involving the acetylation of aminobenzoic acid has already been found to be a very good liver function test, although not as yet developed into a routine clinical method<sup>4</sup>. This fact will be referred to again later on.

According to the teaching of Metchnikoff, a man is as old as his arteries, in other words, the expectation of a man's life is inversely proportional to his blood pressure. According to him, blood pressure of the high tension type as well as practically all the other ills that flesh is heir to seemed to depend on the amount of bacterial decomposition in the gastro-intestinal tract, and of the possible harmful products resulting from this decomposition he considered chiefly those derived from protein material. In fact, he regarded the production of acid through the bacterial decomposition of carbohydrate material as decidedly beneficial, seeing that the acid thus formed inhibited the action of proteolytic organisms which flourish only in a mildly alkaline medium. In the past, the work carried on at our laboratory has been largely directed along lines of this nature. Thus, we have been interested in studying these various putrefactive products both as regards their method of formation and their quantitative estimation, and we have given particular attention to the methods by which various toxic substances are detoxicated or

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<sup>1</sup> From the chemical research laboratory of Fordham University

1 Major, R H. *Am J M Sc* **170** 228 (Aug.) 1925

2 James, A A, Laughton, N B, and McCallum, A B. *Science* **62** 181, 1925

3 Sherwin, C P. *Physiological Rev* **2** 238 (April) 1922

4 Vesell, Harry, and Sherwin, C P. *Testing of Liver Function, Detoxication by Liver*, *Arch Int Med* **37** 257 (Feb.) 1926

rendered innocuous by the animal organism. By far the best known putrefactive products derived from protein decomposition in the gastrointestinal tract are indol, skatol and phenol. Of these indol is the most notorious, some of it is detoxicated in the animal or human body by its chemical combination with acid potassium sulphate, the resulting compound being known as indican, which is then excreted in the urine. The unaltered and uncombined fraction of the indol is excreted in the feces, and is partly responsible for the unpleasant odor of fecal discharges. Under the heading indican one may read literally thousands of pages of clinical, chemical and physiologic literature. If not directly the cause of insomnia, melancholia, chorea, various kinds of insanity, and several other less well defined constitutional disturbances, it is at least certain that indican has actually been found in large amounts in the urine in a majority of such cases by different investigators at various times. We have shown in a previous article<sup>5</sup> that the accepted clinical methods for determining indican in the urine, such as the methods of Obermayer or of Jolles, are not only not quantitative but give no results that are even comparable under like experimental conditions. What we have said for the determination of urinary indican holds as well for the corresponding compound of skatol, but to a far less extent for phenol. These conclusions were drawn only after human beings as well as rabbits had been fed several doses of indol, skatol and phenol, and the accepted clinical methods of determining these substances had been checked against the increased output of ethereal sulphates and of glycuronic acid, which afford a more accurate although less convenient index of the amounts of the substances in question. Besides this, we found that as much as 50 mg of skatol or of indol might be ingested by an adult human being without any untoward results, but that the ingestion of more than this quantity produced the typical symptoms met with in cases of marked constipation, such as nausea, loss of appetite, headache, melancholia and sleeplessness. Vomiting was prevented by coating the gelatin capsules with salicin so that the contents might not be loosed in the stomach, but rather in the intestine.

It must be borne in mind that from a chemical standpoint there are two varieties of putrefaction products, those containing nitrogen and those containing no nitrogen. The nitrogenous putrefaction products are formed by the action of certain bacteria which remove carbon dioxide from the acid group of the protein derivatives present in the gastrointestinal tract, and compounds are thus formed known chemically as amines which are of particular physiologic interest on account of their reputed marked toxicity. In the formation of the non-nitrogenous putrefaction products, nitrogen is first removed from the amino-acids of the

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<sup>5</sup> Novello, N. J., Wolf, M., and Sherwin, C. P. *Am. J. M. Sc.* **170** 888 (Dec.) 1925.

decomposing protein molecule, and a compound is left behind which is acidic in character and which contains only carbon, hydrogen and oxygen. This type of compound is in general much less harmful from a physiologic standpoint than the nitrogen containing compounds. The work done at our laboratory on the latter compounds has been to prepare a number of these putrefaction products in the laboratory and to feed them in varying amounts, then to study not only their relative toxicity but also the method by which they might be detoxicated.

Taking human beings as subjects, we administered to them varying doses of the chemically pure putrefaction products which we had previously prepared in the laboratory. These substances were administered for the most part on a fairly empty stomach or just before the evening meal, this being the heaviest meal of the day. The protein decomposition products of acid character were usually ingested in the form of a

*Fate of Some Protein Putrefactive Products in the Human Body*

Name of Compound Fed	Fed in 24 Hours	Excreted Unchanged	Oxidized	Combined With	Excreted in Urine Chiefly in Form of	Percentage of Total Dose Recovered in Urine
Nitrogen free substances						
Benzoic acid	20	Partly	No	Glycocoll	Hippuric acid	80
Phenylacetic acid	16	Partly	No	Glutamine	Phenylacetyl glutamine	50
Phenylpropionic acid	12	Partly	Yes	Glycocoll	Hippuric acid	90
Parahydroxybenzoic acid	20	Entirely	No		Unchanged	70
Parahydroxyphenylacetic acid	8	Entirely	No		Unchanged	75
Parahydroxyphenylpropionic acid	16	Partly	Yes		Unchanged	65
Nitrogen containing substances						
Indoleformic acid	6	Entirely	No		Unchanged	80
Indolacetic acid	4	Entirely	No		Unchanged	90
Phenylethylamine	1	?	Yes		Phenylacetic acid	50
Tyramine	1	?	Yes		Parahydroxyphenylacetic acid	60
Indolethylamine	1	?	Yes		Indolacetic acid	60

water solution of the sodium salt prepared by adding the substance to a solution of sodium carbonate until neutrality to litmus was obtained. The nitrogenous substances, on the other hand, were easily dissolved in water by adding at the same time a little dilute inorganic acid such as hydrochloric acid, thereby forming the soluble salt of the amine. It was not desired to feed the material in capsules because thus all the substance would be deposited either in the stomach or intestine at one time and in a very localized region, thereby more than likely causing a local irritation of the mucous membrane and simply hindering the rapid absorption of the substance. If ingested as solution, the substance would be gradually liberated by the acid gastric juice if it were in an alkaline solution, and would undergo much the same process in the

intestine if in acid combination. The urine was voided immediately after ingestion of a dose of the substance and then all the urine was collected in twenty-four hour periods. The evaporated urine was then acidified, extracted with some organic solvent such as alcohol, ether or ethyl acetate. The feces were not examined for the unchanged compound, as the dosage was small and the compound should have been largely absorbed from the gastro-intestinal tract, besides, we were chiefly interested in the process by which the human body detoxicates these poisonous compounds.

In the accompanying table may be seen the names as well as the relative toxicity of the compounds fed. The figure in the left hand side of the table shows the maximum dosage that the human body is able to dispose of in the course of twenty-four hours when the total amount is divided into equal doses and ingested at six hour intervals.

#### COMMENT

The amino-acids that are chiefly concerned in the putrefactive decomposition of proteins or, in other words, those components of the protein molecule from which are derived the most undesirable putrefactive products are tryptophane, tyrosine and phenylalanine. Phenylalanine, after losing its nitrogen containing amino group according to the first set of reactions forms phenylpropionic acid, then phenylacetic acid, and lastly benzoic acid, by losing respectively one, two and three carbon atoms through the action of bacterial decomposition. Tyrosine, which is parahydroxyphenylalanine, in a similar manner forms, according to these reactions, parahydroxyphenylpropionic acid, parahydroxyphenylacetic acid, and parahydroxybenzoic acid. Tryptophane forms in the same way indolpropionic acid, indolacetic acid, and indolformic acid, when the acid joined to the indol has respectively three, two, and one carbon atom. We were unable to prepare indolpropionic acid in sufficient amounts for the experimental work so we were limited to the use of indolacetic and indolformic acid.

The scheme for the detoxication of these nonnitrogenous compounds is in general the same in the human as in the animal body. There is first an attempt on the part of the organism to oxidize or burn up the foreign molecule, but as each of these compounds is a coal tar derivative it contains a benzene nucleus which is highly resistant to the oxidative mechanism, so only a part of the molecule is burned, that is, the aliphatic part or "side-chain", then the oxidation ceases. For instance, phenylpropionic acid loses two carbon atoms and is thus changed into benzoic acid. If the compound is entirely nontoxic it is excreted free in the urine as the sodium salt. The remainder of these acids are to some degree toxic and are therefore detoxicated by joining them to glycine or amino-acetic acid, with the exception of phenylacetic acid, which is joined to glutamine. It is an interesting fact that the human body, like

the animal, can synthesize one of the protein constituents (the glycine) out of refuse material (the urea nitrogen) when it needs the glycine for detoxication purposes, but the human, *unlike* the animal, can also synthesize a second amino-acid (glutamine) from the same source for defensive purposes <sup>6</sup>

While considerable is known regarding the non-nitrogenous protein decomposition products in the body, little is known as to the fate of the nitrogen containing molecules. We know, however, that they are much more toxic than the other non-nitrogenous compounds. We therefore employed the amines derived from the same three amino-acids already mentioned, namely, tryptophane, phenylalanine and tyrosine, these amines are called, respectively, indolethylamine, phenylethylamine and tyramine. We found that, as was expected, the compounds were much more toxic than the non-nitrogenous protein derivatives, but in the long run they were by no means as toxic as had ordinarily been thought. In each of these compounds we find the same coal tar or aromatic nucleus with a side chain of two carbon atoms and a nitrogen atom. In the detoxication of these basic compounds the first step seems to be the splitting off of the nitrogen of the amino group and the conversion of the compound into the corresponding alcohol which after oxidation is finally converted into a non-nitrogenous compound of an acid nature, in this case into an acetic acid derivative, namely, indolacetic or else phenylacetic acid. This reduces the toxicity to about 3 per cent of the corresponding nitrogenous compound.

The site or location of this detoxication process in the body is a question that has aroused considerable interest and has called forth several different hypotheses. The work of Kingsbury <sup>7</sup> has shown that benzoic acid is largely conjugated with glycocholic acid by the kidney in a normal person but that in the case of lowered kidney function the work of detoxication may to a large degree be taken over by the liver. In our own laboratory we <sup>8</sup> have found that certain aniline derivatives are detoxicated in the human body by joining them with acetic acid. This is true only in the case of normal human beings, and the reaction is very limited in the case of persons with damaged livers. In fact, this is so much the case that the extent of acetylation after the ingestion of one of these aniline-like compounds seems to be a good indication of the efficiency of hepatic function. Koessler and Hanke <sup>9</sup> have shown in their work on histamine that the gastro-intestinal wall very likely is the seat of some detoxicating mechanism, while other experimenters, after

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6 Sherwin, C. P., Wolf, M., and Wolf, W. *J. Biol. Chem.* **37** 113 (Jan) 1919. Shiple, G. J., and Sherwin, C. P. *J. Am. Chem. Soc.* **44** 618, 1922.

7 Kingsbury, F. B., and Bell, E. T. *J. Biol. Chem.* **21** 297, 1915.

8 Muenzen, J. B., Cerecedo, L. R., and Sherwin, C. P. *J. Biol. Chem.* **67** 469, 1926.

9 Koessler, K. K., and Hanke, M. T. *J. Biol. Chem.* **59** 889 (April) 1924.

passing blood through the surviving livers of dogs noted that the aromatic amines (of the type we have used in this experiment) if dissolved in the ingoing blood could be accounted for after passing through the liver as the corresponding acid. There are therefore three possible or even probable places where this detoxication takes place—the liver, the kidney, and the wall of the gastro-intestinal tract. It seems most probable, however, that the two latter named possibilities are only of minor importance, thus leaving the liver as the most probable site of general detoxication.

In consideration of the relative toxicity of these compounds we may safely say that their importance from this standpoint has been greatly exaggerated. For example, when we consider that the average daily output of benzoic acid (in the combined form of hippuric acid) amounts to but 0.3-0.6 Gm. per day, and that perhaps most of this is of endogenous origin, we must conclude that this putrefactive product is of only moderate importance. The quantity of the other non-nitrogenous constituents of the urine is negligible. Even in the case of persons suffering from severe auto-intoxication, many liters of the urine must be collected before even traces of the other compounds of this type, such as phenylacetic acid, parahydroxyphenylacetic acid, phenylpropionic acid and parahydroxybenzoic acid, can be found. Large doses such as were administered in the course of this experiment did not lead to the classical symptoms supposedly due to the overproduction of putrefactive products in the intestine, symptoms such as irritability, loss of appetite and sleeplessness. On the contrary, there appeared an increased appetite and general slowing up of cerebral function, along with a feeling of drowsiness.

The toxicity of the nitrogen containing products of protein decomposition is, however, a different question. These are from twenty to one hundred times as toxic as the non-nitrogenous compounds. They produce much more of a general reaction, usually a feeling of nausea with temporary loss of appetite, high nervous tension and sleeplessness, followed usually in a short time by a feeling of impending evil and always by a severe diarrhea. There is a slight elevation of temperature and increased pulse rate, with rise in arterial tension. It seems to us, however, that even the importance of this type of putrefactive product has been somewhat overestimated. Its toxicity depends chiefly on the rapidity of its absorption as compared to the considerable period of time necessary for its detoxication.

The human body it would seem is equipped with a chemical defense mechanism that is capable of detoxicating the various types of putrefactive products formed within the intestines, and at the same time is able to cope with larger quantities of these products than are normally present within the intestine. The human body follows in general the same line of chemical defense as does the lower animal, that is, the destruction

of an organic poison by means either of oxidation or reduction. In case these means fail, the compound is detoxicated by combining it with another compound or organic radical. Several of these compounds used in detoxication, such as glycocholic acid, glutamine, acetic acid and glucuronic acid, although not stored in the body for emergency purposes, can be synthesized in considerable quantities when necessary for this purpose. The human body is different from that of the lower animals in that it employs glutamine in one of its detoxication processes—a compound used by none of the lower animals so far investigated.

#### SUMMARY AND CONCLUSIONS

1 There are two general classes of decomposition products formed from protein in the lower intestine due to bacterial action, namely, the non-nitrogenous and the nitrogenous or amino derivatives.

2 We prepared the principal non-nitrogenous putrefactive products of the three amino acids, phenylalanine, tyrosine and tryptophane, namely, benzoic acid, phenylacetic acid, phenylpropionic acid, parahydroxybenzoic acid, parahydroxyphenylacetic acid, parahydroxyphenylpropionic acid, indolformic acid and indolacetic acid.

3 These non-nitrogenous putrefactive products were fed to human beings in order to determine their toxicity, then the urine was examined in order to identify the detoxication product and hence the method of detoxication by the body.

4 Phenylpropionic acid was oxidized to benzoic acid, which was then combined with glycocholic acid and excreted as hippuric acid. Phenylacetic acid was excreted in combination with glutamine. The other acids were excreted uncombined. In the table is found the maximum dosage of each, also the amount recovered from the urine.

5 Of the nitrogenous or amino derivatives of the foregoing amino acids, namely, phenylethylamine, tyramine and indolethylamine, all three were prepared and fed in 1 Gm amounts during a period of twenty-four hours.

6 These amino compounds proved much more toxic than the non-nitrogenous substances. They were detoxicated by the body by splitting off the nitrogen, thus converting them into the acidic compounds of the type mentioned above.

7 The site of these detoxication reactions would appear to be chiefly the liver, but to some extent this function may be performed by the kidney or the gastro-intestinal wall.

8 The human body is apparently provided with a chemical defense mechanism nonspecific in character which is more than adequate for the detoxication of the small amount of putrefactive products normally produced in the human intestine by the action of putrefactive bacteria on unabsorbed protein material.

# DIABETES

## A STATISTICAL STUDY OF ONE THOUSAND CASES \*

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Statistical studies of a large series of individual cases of any disease offer considerable information, especially in regard to phenomena of its various stages, the incidence of different phases and their inter-relationship. In particular, such a review enables one to see his mistakes and gives an opportunity to alter management accordingly. For these reasons I am offering this review of 1,000 consecutive cases of diabetes which have been under observation during the last five years. This study covers the period from March 1, 1921, through August, 1925, when the one-thousandth case was seen. The total number of patients admitted to the Cleveland Clinic during this period was 55,939, thus, the incidence of diabetes to all other diseases among our patients is nearly 1.8 per cent.

### AGE AND SEX INCIDENCE

Chart 1 shows the distribution of these cases according to sex and in different age decades. It will be noted that there is a strikingly increased incidence in the fifth, sixth and seventh decades, but that there is no significant difference in the sex incidence in any decade. It is not strange that, as middle age approaches and is passed, the organism shows some signs of imperfect or markedly diminished carbohydrate metabolism, just as at this period the beginning failure of other functions is shown by the development of myocarditis, chronic nephritis and hypertension in greater frequency than in earlier years. That the development of diabetes in later life is part of the general degenerative process which affects sometimes one and sometimes another organ, according to the relative degrees of resistance, is indicated by the fact that when diabetes is inaugurated at this time it is usually of a milder degree than when it is of earlier onset.

In chart 2 I have summarized the incidence of diabetes by decades, according to the data of ten different authors, as cited by Joslin,<sup>1</sup> and in table 1 are given data from the seven observers whose work he reviews. A more specific classification by individual years from 1 to 30 has been prepared in table 2, which emphasizes the fact that diabetes occurs in the earliest years, although the percentage of incidence increases when the totals for each decade are considered.

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\* From the Medical Division, Cleveland Clinic

1 Joslin, E. P. The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 123

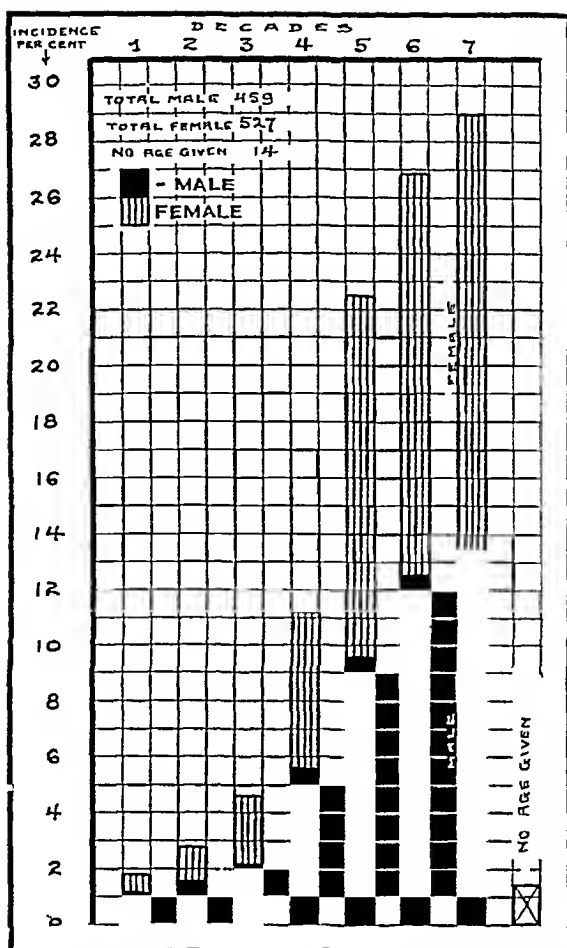


Chart 1—The sex and age incidence of diabetes (from author's series of 1,000 cases)

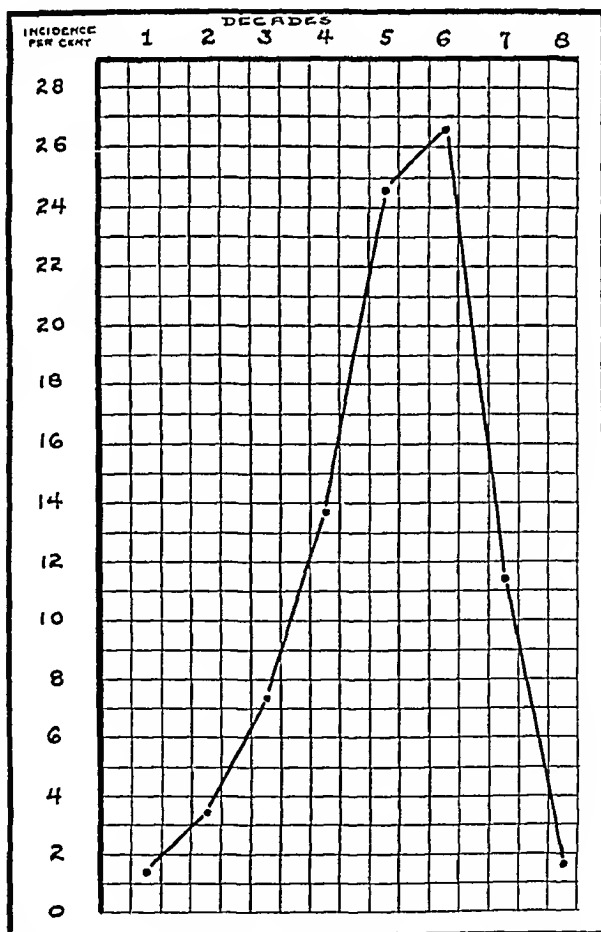


Chart 2—The average incidence of diabetes in different age decades (compiled from the literature)

TABLE 1—*Incidence of Diabetes According to Age Decades (Compiled from the Literature)*

	Decades							
	I	II	III	IV	V	VI	VII	VIII
Frerichs	1	7	10	18	25	26	11	1
Seegen	0.5	8	16	16	21	30	10	0.5
Grube		17	28	11.2	23.1	39.5	18.1	3.4
Schmitz	0.83	4.1	9.3	17.3	22.3	32.6	10	3.3
Pavy	0.58	4.19	7.13	16.4	24.9	30.7	13.4	2.5
Kulz	1	8	4.6	17.2	36	26.8	9.2	0.1
Von Noorden		0.43	2.4	10	21	17.7	4	0.4
Von Noorden	1.43	2.43	6	9.57	12.5	11	2.1	

Light cases  
Severe and  
moderately severe

Umber reports eleven children in his last series of 200 cases of diabetes

TABLE 2—*Incidence of Diabetes in the First Three Age Decades (From Author's Study of One Thousand Cases of Diabetes)*

Year	Number of Male Patients	Number of Female Patients	Total Number of Patients	Percentage of 1,000 Cases
1	1	1	2	0.2
2	2	1	3	0.3
3	1		1	0.1
4		1	1	0.1
5	1	1	2	0.2
6		1	1	0.1
7	2		2	0.2
8		1	1	0.1
9	2	1	3	0.3
10	2		2	0.2
11	3	1	4	0.4
12	1		1	0.1
13	1		1	0.1
14	1	1	2	0.2
15	4		4	0.4
16	2		2	0.2
17	1	3	4	0.4
18	2	4	6	0.6
19		1	1	0.1
20	1	2	3	0.3
21		4	4	0.4
22	5		5	0.5
23		3	3	0.3
24		1	1	0.1
25		4	4	0.4
26	3	5	8	0.8
27	3	5	8	0.8
28	6		6	0.6
29	2	1	3	0.3
30	1	1	2	0.2

TABLE 3—*The Heredity Factor in the Incidence of Diabetes (After Joslin<sup>\*</sup>)*

Author	Date of Compilation	Number of Cases	Percentage of Cases with Hereditary or Familial History of Diabetes
Grube			8.0
Frerichs		400	9.8
Seegen			14.0
Schmitz			20.0
Kulz		692	21.6
Williamson		500	22.0
Bouchard			25.0
Naunyn	1905	398	17.0
Von Noorden	1917		25.4
Joslin	1923	2,800	21.0

Hereditary 18.5  
Familial 6.9  
Hereditary 15.0  
Familial 7.0

\* Joslin, E. P. The Treatment of Diabetes Mellitus, p. 128

## HEREDITY

The rôle of heredity in the production of diabetes is mentioned by all writers on this subject. In table 3 I have compiled the observations of various observers in order to compare my own results, as given in table 4, with theirs. The percentages given in this list make one feel that heredity must play some part in the incidence of diabetes.

While the percentage of diabetic cases in which one can trace either a familial or a hereditary connection is fairly large, nevertheless it would seem that the factor of environment plays a more important rôle in this group of cases. In a large percentage of cases in this group, the patients were either obese or at least overweight. We do not know the state of

TABLE 4—*The Heredity Factor in the Incidence of Diabetes (From Author's Study of One Thousand Cases of Diabetes)*

	Cases	Percentage of Total Series
Familial history	51	
Hereditary history	46	
Total	97	9.7

TABLE 5—*Blood Sugar in Nine Hundred and Thirty-Three Cases of Diabetes on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar, Mg per 100 Cc	Number of Cases	Blood Sugar, Mg per 100 Cc	Number of Cases
120	51	400	57
150	179	450	33
200	203	500	25
250	138	600	15
300	119	700	12
350	101		

the pancreas at birth, since of course systematic data from personal observations are lacking on this point, so definite conclusions cannot be drawn. Moreover, in families in which there is a familial or hereditary history of diabetes, we do not know how many subjects do not develop diabetes, regardless of their habits, and what is the proportion of these to those who do develop diabetes. Family histories that offer a striking picture of the incidence of diabetes in several generations have been reported in the literature. But such reports are rare, and diabetes itself has such a high incidence that if heredity is an important factor, a closer relationship should be established than has thus far been done. The important points are that, whatever the familial or hereditary incidence of diabetes, if one lives moderately and stays thin, diabetes will not develop, and that, on the other hand, obesity and overindulgence often lead to diabetes even when there is no hereditary history of the disease.

## BLOOD SUGAR CONTENT AND GLYCOSURIA

In this series of diabetic patients, the blood sugar on admission varied from 120 to more than 900 mg per hundred cubic centimeters of blood. The lower figures were found either in early cases or in cases in which the blood sugar was being controlled by proper diet or by diet plus insulin. Table 5 shows the distribution of the cases in this series at the different blood sugar levels. It will be noted that in a large majority of these cases the blood sugar content ranged from 150 to 350 mg per hundred cubic centimeters, but, while higher figures occur less frequently, they are far from being exceptional.

TABLE 6—*Blood Sugar Without Glycosuria in Two Hundred Cases of Diabetes on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar, Mg per 100 Cc	Number of Cases	Blood Sugar, Mg per 100 Cc	Number of Cases
120	20	200	10
130	14	210	4
140	33	220	8
150	31	230	7
160	24	260	4
170	18	270	1
180	15	310	1
190	10		

TABLE 7—*Blood Sugar with Glycosuria in Three Hundred and Ninety-Two Cases of Diabetes on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar, Mg per 100 Cc	Number of Cases	Blood Sugar, Mg per 100 Cc	Number of Cases	Blood Sugar, Mg per 100 Cc	Number of Cases
120	8	230	17	330	11
130	4	240	11	310	15
140	7	250	14	350	14
150	15	260	12	360	5
160	8	270	16	370	5
170	12	280	18	380	10
180	13	290	16	390	7
190	11	300	16	400	6
200	15	310	9	500	35
210	15	320	17	600	19
220	8				

Table 6 offers us an instructive study of the relationship of glycosuria to hyperglycemia in cases of diabetes. The highest blood sugar figure in which glycosuria was not present was 310 mg per hundred cubic centimeters. This table shows clearly that in these cases of diabetes the permeability of the kidney to sugar certainly is lessened, the threshold raised.

Table 7 shows the incidence of glycosuria at the different blood sugar levels.

Some of the highest blood sugar values that I have seen reported in the literature are listed in table 8. The highest blood sugar content seen in any of my patients on admission was in the case of a man,

aged 47, a bricklayer, who had had all the classic signs of diabetes for nearly a year but had had no treatment. He was losing weight and strength daily but did not give up work, and when he came to me his blood sugar was 908 mg per hundred cubic centimeters, and he had a glycosuria of 10 per cent. Some of the other high blood sugar values observed in patients on admission were 732, 652, 696, 600, 778 (coma), 810 (coma), 696, 638, 652, 810 and 732. Such a list seems surprising, but it should be remembered that while an extremely high blood sugar content proves the presence of diabetes, it does not always produce some of the usual signs, such as dryness of the mouth and tongue, extreme thirst, blurring of vision and loss of weight. Often, therefore, persons with a high blood sugar content are comparatively comfortable, with the

TABLE 8—*Highest Blood Sugar Values in Diabetic Patients Reported by Various Observers (Compiled from the Literature)*

Author	Blood Sugar, Mg per 100 Cc	Patient's Condition
Pitfield, R. L. (M. J. & Record 120:433, 1924)	1,700	Coma
Joslin, E. P. (Treatment of Diabetes Mellitus, p. 173)	1,370	Coma
Foster, N. B. (J. A. M. A. 84:719, 1925)	1,260	Coma
	890	Coma
Paddock, B. W. (J. A. M. A. 82:1855, 1924)	1,040	Coma
Liefmann and Stern (cited by Bang, I. Der Blutzucker, p. 135)	1,010	Coma
Weiland, W. (Klin. Wchnschr. 2:736, 1923)	940	Coma
Chapin and Myers (Am. J. Dis. Child. 18:555, 1919)	790	
Author's cases	908	
	910	
	810	Coma
	778	Coma
	732	
	732	

exception of thirst and frequency of urination, and are unconscious of their true condition.

The highest blood sugar figure that I have ever obtained was in the case of a patient in coma in which, immediately after the intravenous administration of insulin and glucose, the blood sugar content was 2,610 mg per hundred cubic centimeters, having been 405 mg per hundred cubic centimeters immediately before the administration. On another occasion in the same case, the blood sugar was 1,108 mg per hundred cubic centimeters following, and 79 mg per hundred cubic centimeters immediately before, intravenous medication. This patient has had three attacks of coma, each due to an indiscretion in diet, yet she is in better health and more active today than she has been for many years, as a result of the continued use of large doses of insulin.

#### TREATMENT WITH INSULIN

There seems to be a general impression on the part of the public that insulin treatment is to be avoided if possible, for it is the prevalent opinion that if insulin is taken once, its use must be continued indefinitely.

TABLE 9—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance (From Author's Study of One Thousand Cases of Diabetes) \**

Age of Patient	Duration of Diabetes	Duration of Insulin Treatment	Period Since Discontinuance of Insulin	Blood Sugar Content When Insulin Was Started	Present Blood Sugar Content
18	3 weeks	31 months	2 months	261	110
23	1 year	6 months	2 months	250	97
26	1 year	4 months	2 months	400	134
28	Recent	5 months	11 months	241	89
32	1 month	45 days	1 month	400	82
38	1 year	15 days	2 months	344	123
39	1 year	16 days	4 months	340	161
40	8 years	75 days	7 months	266	155
42	2 months	60 days	10 months	154	132
43	3 years	16 months	1 month	323	100
43	1 month	5 months	11 months	238	111
44	4 months	4 days	25 months	297	107
44	3 years	17 months	1 month	410	79
44	2 years	16 days	5 months	261	126
45	8 9 years	7 days	34 months	206	172
45	Recent	14 days	22 months	275	138
45	1 month	60 days	5 months	428	106
46	2 years	7 days	21 months	319	104
47	2 years	7 days	23 months	176	90
47	4 years	12 days	4 months	400	110
49	Recent	2 days	14 months	176	125
50	1 year	2 days	17 months	290	76
50	6 years	5 days	23 months	353	133
50	1 year	13 days	23 months	211	130
53	6 weeks	8 days	11 months	353	179
53	2 years	5 days	21 months	227	106
53	Recent	14 days	3 months	280	142
53	1 year	1 month	21 months	202	125
53	Recent	6 days	33 months	200	129
54	Recent	12 days	13 months	384	111
55	2 years	8 days	24 months	467	105
55	6 months	6 days	17 months	163	87
55	2½ months	3 days	5 months	440	60
55	Recent	12 days	25 months	282	80
55	3 4 months	40 days	1 month	169	98
56	1 year	14 days	7 months	454	116
56	1 year	15 days	3 months	391	165
56	4 years	6 days	7 months	167	128
57	4-5 years	14 days	17 months	234	131
57	10-12 years	12 days	18 months	227	117
58	2 years	6 months	13 months	243	122
59	7 9 years	10 days	19 months	294	152
60	Recent	6 days	17 months	182	133
61	3 years	2 days	34 months	194	113
61	7 years	2 days	34 months	232	117
61	5 months	8 days	3 months	344	168
61	1 year	12 days	23 months	333	129
62	Recent	5 days	15 months	243	98
62	1 year	30 days	13 months	222	118
62	1½ years	12 days	12 months	258	112
62	1 year	2 months	1 month	275	98
65	2 years	3 days	11 months	208	126
65	4 years	11 months	12 months	344	145
66	15 years	20 months	6 months	190	167
68	5 years	11 days	23 months	221	131
70	1 month	5 days	16 months	370	85
74	1 year	5 days	18 months	344	156
79	12 years	2 days	5 months	333	116

\* Arranged in order of ages of patients

This is an erroneous conception. It is advantageous to begin treatment with insulin just as soon as the diagnosis of diabetes is established, thus shortening the time the patient must spend at the hospital—an economic advantage both for the patient and for the physician or clinic. Why should one spend a week or ten days on a fasting or a low diet in an attempt to bring a marked hyperglycemia to a normal level if the same end can be accomplished in from twenty-four to forty-eight hours

TABLE 10—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance (From Author's Study of One Thousand Cases of Diabetes) \**

Duration of Diabetes	Age of Patient	Duration of Insulin Treatment	Period Since Discontinuance of Insulin	Blood Sugar Content When Insulin Was Started	Present Blood Sugar Content
Recent	49	2 days	14 months	176	125
Recent	62	5 days	15 months	243	98
Recent	28	5 months	11 months	241	89
Recent	53	14 days	3 months	280	142
Recent	54	12 days	13 months	354	111
Recent	60	6 days	17 months	182	133
Recent	53	6 days	33 months	200	129
Recent	45	14 days	22 months	275	138
Recent	55	12 days	25 months	282	80
3 weeks	18	31 months	2 months	261	110
6 weeks	53	8 days	11 months	353	179
1 month	45	60 days	5 months	428	106
1 month	43	5 months	11 months	238	111
1 month	70	5 days	16 months	370	85
1 month	32	45 days	1 month	400	82
2 months	42	60 days	10 months	154	132
2½ months	55	30 days	5 months	440	60
3-4 months	55	40 days	1 month	160	98
4 months	44	4 days	25 months	297	107
5 months	61	8 days	3 months	344	168
6 months	55	6 days	17 months	163	87
1 year	23	6 months	2 months	250	97
1 year	56	14 days	7 months	454	116
1 year	61	12 days	23 months	333	120
1 year	62	30 days	13 months	222	118
1 year	56	15 days	3 months	304	165
1 year	38	15 days	2 months	344	123
1 year	39	16 days	4 months	310	161
1 year	53	1 month	21 months	292	125
1 year	62	2 months	1 month	275	98
1 year	50	2 days	17 months	200	76
1 year	74	5 days	18 months	311	156
1 year	26	4 months	2 months	400	134
1 year	50	13 days	23 months	241	130
1½ years	62	12 days	12 months	258	112
2 years	58	6 months	13 months	243	122
2 years	47	7 days	23 months	176	90
2 years	65	3 days	11 months	208	126
2 years	44	16 days	5 months	261	126
2 years	46	7 days	21 months	319	103
2 years	55	8 days	24 months	467	105
2 years	53	5 days	21 months	227	106
3 years	43	16 months	1 month	323	100
3 years	44	17 months	1 month	410	79
3 years	61	2 days	34 months	194	113
4 years	65	11 months	12 months	344	145
4 years	56	6 days	7 months	167	128
4 years	47	12 days	4 months	400	110
4½ years	57	14 days	17 months	234	131
5 years	68	11 days	23 months	221	131
6 years	50	5 days	23 months	353	133
7 years	61	2 days	34 months	232	117
7½ years	59	10 days	19 months	294	152
8 years	40	75 days	7 months	266	155
8½ years	45	7 days	34 months	206	172
10-12 years	57	12 days	18 months	344	156
12 years	79	2 days	5 months	333	116
15 years	66	20 months	6 months	190	167

\* Arranged in order of duration of diabetes

by means of insulin with a fairly liberal diet? The essential requirements in the treatment of diabetic patients may be briefly summarized as follows

- 1 The blood sugar must be brought to, or near, the normal
- 2 It must be determined whether or not a comfortable, regulated diet alone will suffice to keep the blood sugar normal
- 3 If a sufficient diet alone will not hold the blood sugar in check, then it must be determined how many units of insulin a day are required and how they should be

TABLE 11—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance (From Author's Study of One Thousand Cases of Diabetes) \**

Period Since Discontinuance of Insulin	Blood Sugar Content When Insulin Was Started	Present Blood Sugar Content	Age of Patient	Duration of Diabetes	Duration of Insulin Treatment
1 month	323	100	43	3 years	16 months
1 month	410	79	44	3 years	17 months
1 month	275	98	62	1 year	2 months
1 month	400	82	32	1 month	45 days
1 month	169	98	55	3-4 months	40 days
2 months	250	97	23	1 year	6 months
2 months	344	123	38	1 year	15 days
2 months	400	134	28	1 year	4 months
2 months	261	110	18	3 weeks	31 months
3 months	344	168	61	5 months	8 days
3 months	394	165	56	1 year	15 days
3 months	280	142	53	Recent	14 days
4 months	340	161	39	1 year	16 days
4 months	400	110	47	4 years	12 days
5 months	428	106	45	1 month	60 days
5 months	261	126	44	2 years	16 days
5 months	440	60	55	2½ months	30 days
5 months	333	116	79	12 years	2 days
6 months	190	167	63	15 years	20 months
7 months	454	116	56	1 year	14 days
7 months	167	128	56	4 years	6 days
7 months	266	155	40	8 years	75 days
10 months	154	132	42	2 months	60 days
11 months	241	89	28	Recent	6 months
11 months	208	126	65	2 years	3 days
11 months	238	111	43	1 month	5 months
11 months	333	179	53	6 weeks	8 days
12 months	258	112	62	1½ years	12 days
12 months	344	145	65	4 years	11 months
13 months	243	122	58	2 years	6 months
13 months	222	118	62	1 year	30 days
13 months	384	111	54	Recent	12 days
14 months	176	125	49	Recent	2 days
15 months	243	98	62	Recent	5 days
16 months	370	85	70	1 month	5 days
17 months	182	133	60	Recent	6 days
17 months	163	87	55	6 months	6 days
17 months	234	131	57	4 5 years	14 days
17 months	290	76	50	1 year	2 days
18 months	344	156	74	1 year	5 days
18 months	227	117	57	10-12 years	12 days
19 months	294	152	69	7 9 years	10 days
21 months	319	104	46	2 years	7 days
21 months	292	125	53	1 year	1 month
21 months	227	106	53	2 years	5 days
22 months	275	138	45	Recent	14 days
23 months	333	129	61	1 year	12 days
23 months	176	90	47	2 years	7 days
23 months	221	131	68	5 years	11 days
23 months	353	133	50	6 years	5 days
23 months	241	130	50	1 year	13 days
24 months	467	105	55	2 years	8 days
25 months	297	107	44	4 months	4 days
25 months	282	80	55	Recent	12 days
33 months	200	129	53	Recent	6 days
34 months	194	113	61	3 years	2 days
34 months	232	117	61	7 years	2 days
34 months	206	172	45	8-9 years	7 days

\* Arranged in order of periods since discontinuance of insulin

distributed in relation to the diet 4 The patient must be taught the essential diabetic diet, and, if insulin is required, how to administer it to himself

It has been generally stated that in children one is not able to cut down the insulin dosage, but rather that this has to be increased This is in accordance with my own experience The limits of safety for a child are much narrower than for adults, and a good clinical result is

much more easily spoiled. On the other hand, in adults there are many cases in which in time the insulin can be discontinued, the patient continuing to be well and keeping a normal blood sugar on diet alone. In tables 9, 10 and 11 the results of the administration of insulin are summarized in a series of cases in which the period of administration varied from a few days to almost three years. This series disproves the belief on the part of the public that insulin once used must be continued for life.

The rapidity with which the blood sugar can be reduced is well illustrated by the case of a young man, aged 22, whom I first saw on June 24, 1925. For two months he had had the classic symptoms of diabetes, but glycosuria was first discovered four days before I saw him, he had not consulted any physician before that time. The blood

TABLE 12—*Record of Patient (Chart 3)*

Date, 1925	Blood Sugar, Mg per 100 Cc				Insulin Dosage in Units				Diet
	8 a m	12 m	5 p m	7 p m	8 a m	12 m	5 p m	7 p m	
June 25	111	187	181	153	40	10	20	20	100 Gm of carbohydrate 60 Gm of protein 128 Gm of fat 1,800 calories
23	288	312	248		20	20	30		
27	258	234	238		30	30	30		
28	226		163		30	30	30		
29	214		100		30	30	30		
30	227	234			30	30	30		
July 1	217				30	30	30		Discharged from hospital
2	171	183	95		30	30	30		
3	200				20	20	20		
6	173				20	20	20		
To take 3 doses of insulin daily, 20 units each, for 2 weeks, then 2 daily doses of 20 units each									

sugar on admission was 732 mg per hundred cubic centimeters, there were heavy acetonemia and heavy lipemia, with extreme glycosuria and acetonuria. On that day, between 2 and 10 p m, he received hourly intravenous doses of insulin of 20 units each. Chart 3 shows the resultant uniform uninterrupted fall of blood sugar during this period, from 732 to 131 mg per hundred cubic centimeters. The subsequent progress of this patient is shown in table 12.

#### INSULIN REACTIONS

Shortly after the discovery of insulin Banting and his co-workers described the reactions to insulin in rabbits, explaining these as being due to hypoglycemia, which develops several hours after the subcutaneous injection of insulin, and which can be eliminated by the injection of glucose.

In my work it soon became evident, however, that there is no definite relationship between the degree of hypoglycemia and the reaction, for large doses of insulin sometimes produce a reaction a long time after the

blood sugar has reached the value of 45 mg per hundred cubic centimeters or less, and also in the presence of similar hypoglycemia there may be no reaction. Moreover, the injection of calcium will eliminate the reaction without increasing the blood sugar value.

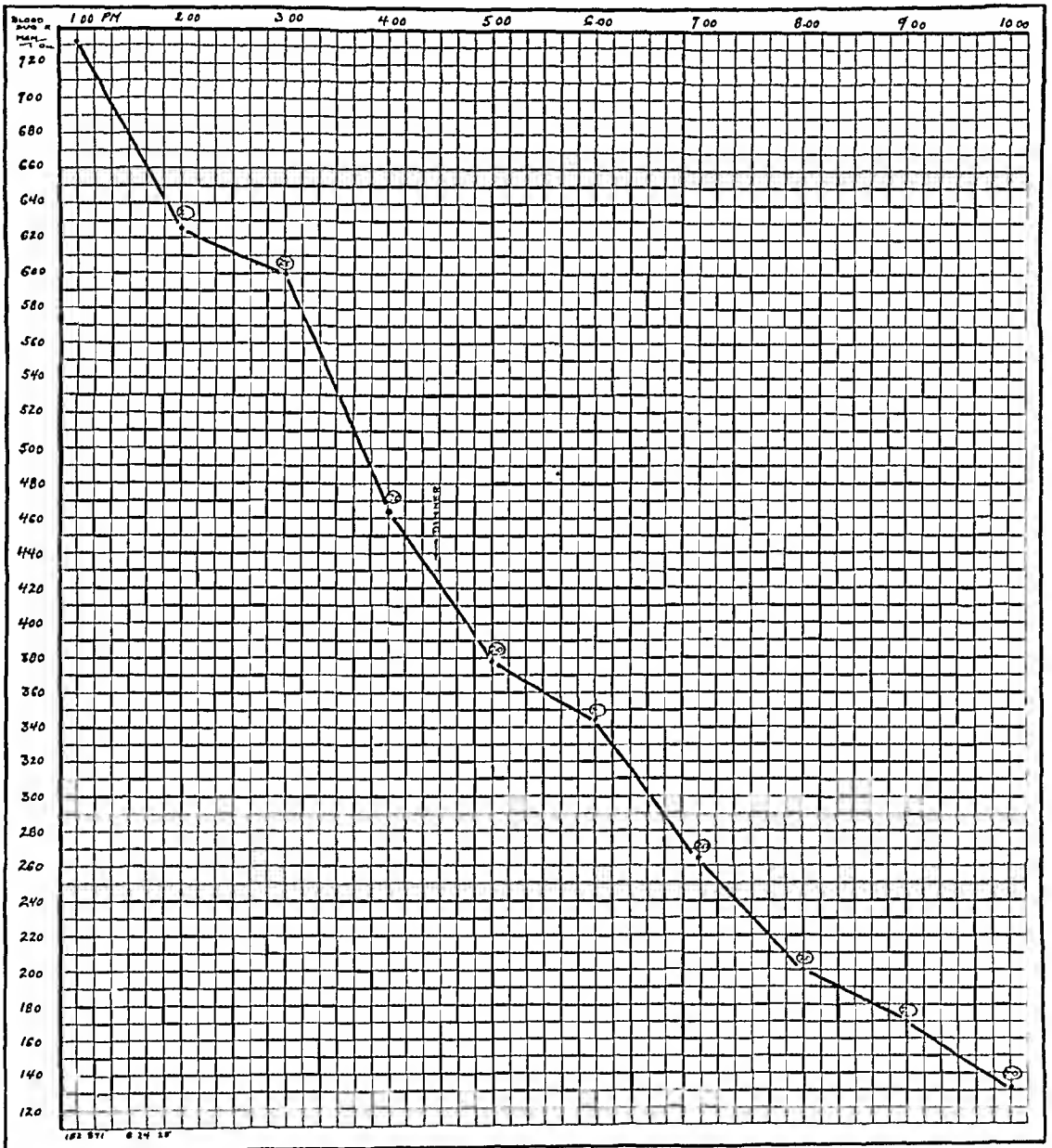


Chart 3—The fall of blood sugar in a diabetic patient following hourly doses of insulin. The insulin dosage is indicated in the circles above the sugar curve.

It may be well at this point to describe the typical symptoms of an insulin reaction. The outstanding symptoms in the usual order of their occurrence are (1) a feeling of anxiety, (2) pallor of the skin, (3) increased pulse rate and slight tremor of the hands, (4) a "sinking spell," the patient feeling weak and exhausted, (5) voracious hunger,

and (6) perspiration all over the body so profuse that the clothing may be drenched. Children will suddenly cry out even from a sound sleep as though terrified, and in children also a marked convergent nystagmus is often seen during a severe reaction. Any or all of these symptoms may appear. In my analysis of all cases in which a reaction occurred, which has included observations of the blood sugar before and at the time of reaction, and of the time interval between the administration of insulin and the reaction, I found that although in about 50 per cent

TABLE 13—*Insulin Reactions Relation of Blood Sugar Before and at Time of Reaction to Dosage of Insulin and the Length of Time Before Reaction Occurred (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar Before Administration of Insulin, Mg per 100 Cc	Insulin Dosage, Units (Lilly)	Blood Sugar at Time of Reaction, Mg per 100 Cc	Time Between Administration of Insulin and Reaction, Minutes
400	20	186	60
102	30	51	45
286	56	246	8
93	42	59	30
153	10	55	60
256	31	67	90
197	20	62	60
167	20	57	95
196	20	125	5
222	12	110	20
40	15	40	Immediate
133	5	61	10
191	16	147	2
184	32	65	120
141	18	53	5
175	20	83	65
104	20	41	60
410	30	394	25
287	20	285	9
288	20	202	10
179	20	122	30

of the cases the reaction apparently was due to hypoglycemia, in nearly 50 per cent the reaction occurred when hyperglycemia was present. I found, moreover, that even in the same patient the reaction to insulin varied. Thus, a patient might have a low blood sugar content on one day and yet show no reaction even to large or repeated doses of insulin, while on another day when the blood sugar of the same patient was at a much higher elevation, a smaller dose of insulin would produce a marked reaction. In certain instances patients with such a marked hypoglycemia as 50 or 60 mg per hundred cubic centimeters have shown no reaction after intravenous injection of from 20 to 40 units of insulin. In the case of one of my patients, a girl, aged 6 years, on one afternoon when the quantity of blood sugar was 38 mg per hundred cubic centimeters (a fact that I did not know at the time) no reaction followed the intravenous injection of 20 units of insulin. It is obvious, therefore, that in many cases these reactions must be due to some other cause than hypoglycemia.

In the latest report from the Czech University at Prague, Mačela <sup>2</sup> states that they have succeeded in manufacturing insulin from which the substance that causes reactions has been chemically removed

In table 13 I have summarized the reactions which have occurred in my own series with reference (1) to the height of the blood sugar

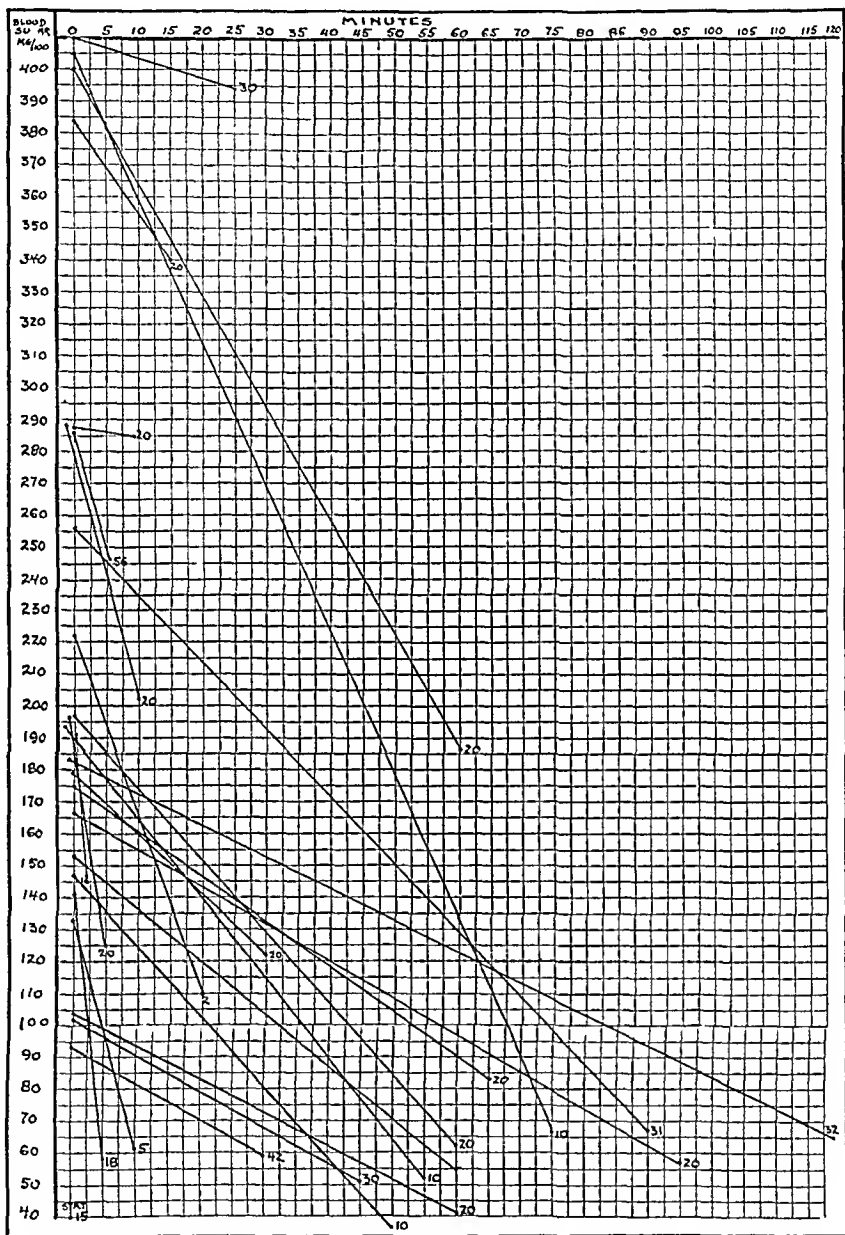


Chart 4—The fall of blood sugar which accompanied reactions to insulin in twenty-four cases, and the length of time between the administration of insulin and the reaction

before the insulin was given, (2) to the dosage of insulin given intravenously, (3) to the blood sugar at the time of the reaction, and (4) to the length of time between the administration of insulin and the reaction

Chart 4 gives the same data in a form that emphasizes the irregularity of these reactions. Thus, a reaction may occur immediately after the insulin has been given, or it may not appear until two hours or more later. The blood sugar content at the time of the reaction may be high, or it may be low. A reaction may follow a small dose of insulin in the presence of a marked hyperglycemia, and again no reaction may follow a large dose (10-40 units) of insulin in the presence of a low hypoglycemia. In other words, it is impossible to draw any general conclusions concerning these reactions as we do not know to what they are due. They certainly are not all due to hypoglycemia.

TABLE 14—*Blood Examinations of Patients in Coma on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar on Admission	Plasma Acetone	Plasma Car- bon Dioxide	Outcome
200	+	40.4	Living
405	+	44.3	Living
434	+	19.2	Living
384	0	21.4	Living
353	+++	27.1	Living
400	++	21.4	Living
460	+++	38.5	Living
778	+++	21.4	Died
810	+++	9.9	Died
447	+		Died
652	+++	17.6	Died
300		25.2	Died
267	+++		Died
333	0		Died

#### COMA

The total number of cases of coma included in this series is fourteen. Seven of the patients are living and seven are dead. Of the seven living patients, two had relapses and were pulled through a second attack, one through a third attack. The seven patients who died were all in a critical condition when they arrived here, and died from one to a few hours after their admission to the hospital.

Fourteen other patients living outside of the city developed coma during the first year after their discharge from the hospital. In all these cases the immediate cause of the coma was an intercurrent infection (boils, an infected finger, tuberculosis) and absolute disregard of the prescribed diet. All these patients died.

The laboratory data on the fourteen cases of coma cited above are given in table 14. It will be noted that in this group of cases the blood sugar content ranged from 200 to 810 mg. per hundred cubic centimeters, the acetone in the blood plasma ranged from 0 to 3 plus, and the carbon dioxide combining power ranged from 44.3 to 9.9 mm., the higher figures being due to the administration of insulin previous to the examination, the results of which are here given.

As for the treatment of patients who are first seen in a state of coma, as long as there is sugar and acetone in the urine one can feel safe in administering an initial dose of from 40 to 60 units of insulin every two hours, or every hour if a heavy glycosuria persists. Liquids should be given by mouth, preferably in the form of dilute lemonade or orange ade, and in large quantities, from 2,000 to 4,000 cc.

Even after a patient has recovered from coma, the administration of insulin should be continued to the extent, perhaps, of three daily doses

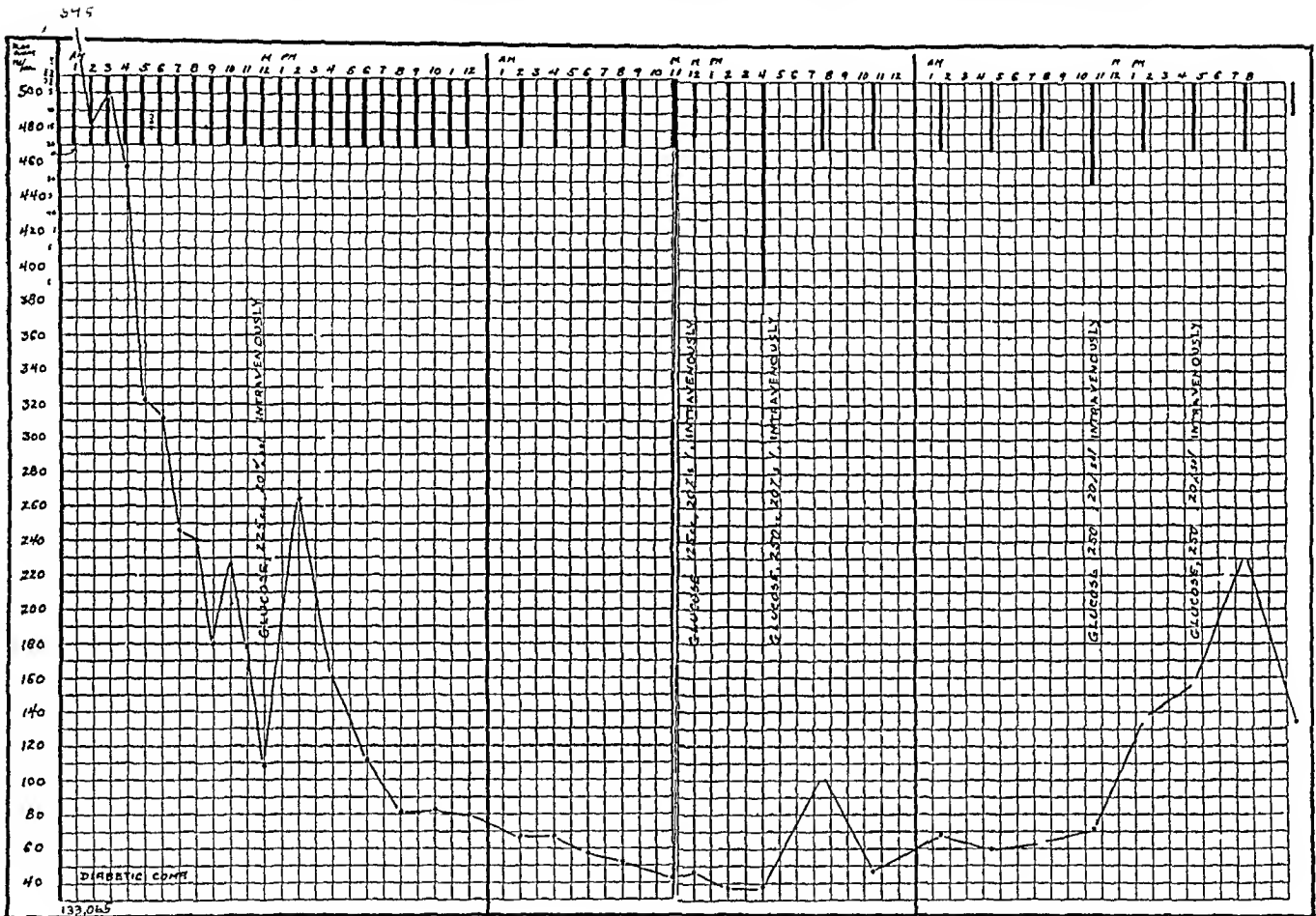


Chart 5—The response of blood sugar to insulin and glucose in a patient in diabetic coma on three successive days

of 20 units each unless reactions occur, in which case the dosage should be diminished accordingly. The diet is, of course, an important factor in the treatment. The intravenous injection of glucose supplies food and liquid which, with the aid of insulin, are properly metabolized, as is shown by the lack of its excretion in the urine. The injection of glucose is especially important in the case of an emaciated and weak person, as it serves to tide the patient over a crisis, but after two or three days the natural feeding by mouth must be relied on. Chart 5 shows the response to insulin and glucose on three successive days in the case of a patient in diabetic coma. Chart 6 shows the response in a case

of diabetes in which a cholecystenterostomy was performed For seven days following the operation nothing was given by mouth, but all the nourishment was given intravenously in the form of a 10 per cent glucose solution in which insulin was incorporated From this chart it can be clearly seen that glucose administered intravenously does not raise the blood sugar level even when continued over a longer period of time Of course, it is true that no other form of nourishment had been given dur-

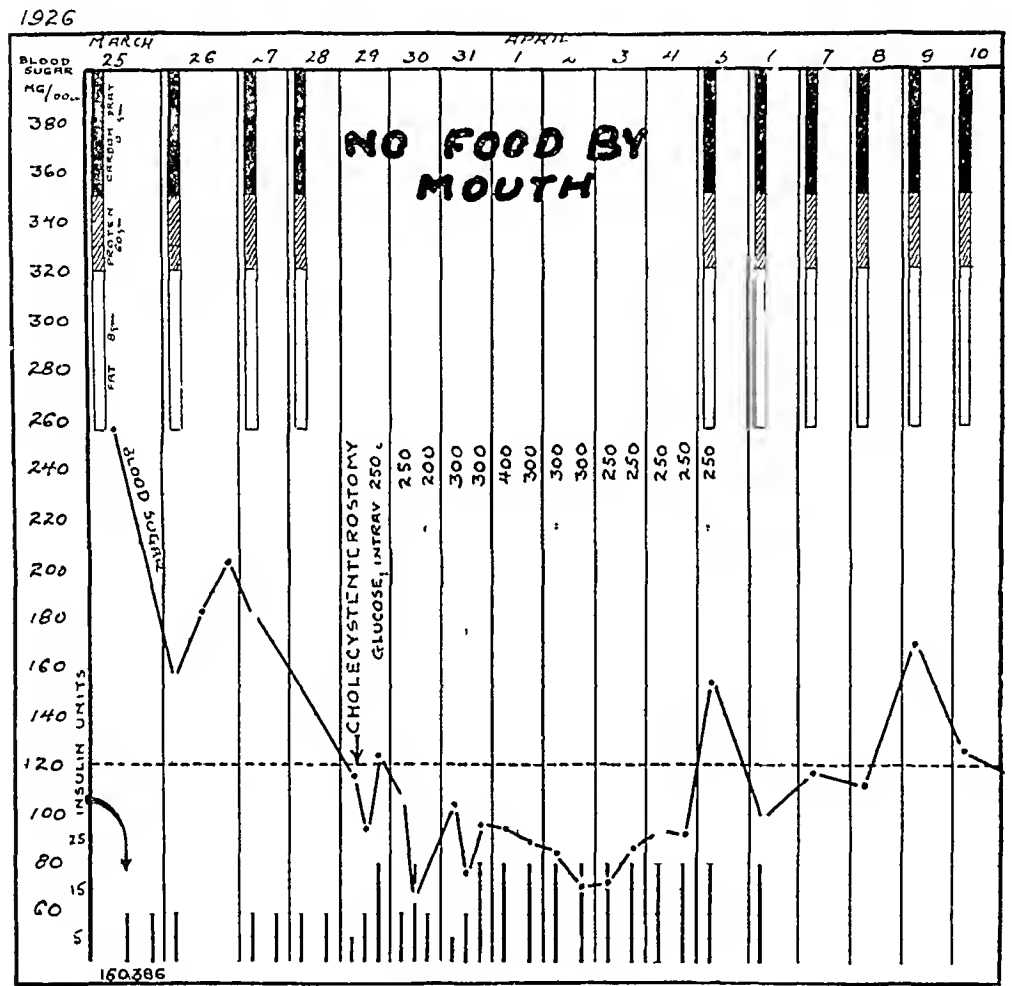


Chart 6—The reaction to insulin in a patient before and after cholecystenterostomy

ing this time, yet I feel that, in spite of this fact, this evidence tends to dispel the fear of administration of glucose solution intravenously In the case of patients who are under treatment at home, repeated intravenous administration of glucose cannot be readily carried out, but a sufficient quantity of liquid can be supplied through a stomach tube after the stomach has been washed out

The severity of the coma in any person may be judged by the degree of stupor, the characteristic forced Kussmaul type of breathing, the

markedly dry mouth and tongue, the flush of the cheeks, the exhaustion of the patient, which is manifested by a subnormal temperature, the failing circulation, which is manifested by the low blood pressure, and the vomiting of green or even hemorrhagic material, which often is profuse. These conditions constitute a terrific drain on the body, and one should try to reestablish the normal status as soon as possible in order to save the dwindling reserves. It should be emphasized that in giving insulin it is better to give too large a dose than one that is insufficient. Up to the present time I have not seen a reaction to insulin in any patient who has been under treatment for diabetic coma, the danger of a reaction practically being eliminated by the intravenous infusion of glucose.

In spite of large intravenous doses of insulin and glucose, and the application of all the other measures at our command, patients in coma die. One can say almost without reservation that they die because treatment is started too late. In coma, in which we are dealing with marked acidosis and with ketone bodies circulating in the blood stream, the heart bears the brunt of the extra load. Moreover, under any circumstances, the heart muscle of a diabetic patient has not the capacity of normal muscle for the storage of glycogen. This means that in an emergency its diminished glycogen supply is soon exhausted. The utilization of glucose even in the presence of a high blood sugar content is well illustrated by table 15. Moreover, the ketone bodies injure the heart muscle further, these two factors being, in part at least, responsible for the low blood pressure. Thus, the overstrained heart muscle, without reserves, and poisoned with the ketone bodies, is likely to give out at any moment. I saw a patient in coma die instantly as the result of an acute dilatation of the heart when she began to struggle in an attempt to get up, although the acidosis was beginning to be under control. The utmost physical rest is therefore extremely important.

Other conditions in which coma occurs which must be differentiated from diabetic coma are septicemia, meningitis, cerebral hemorrhage, uremia, traumatic concussion, morphine poisoning, encephalitis and insulin reaction. The differential diagnosis of diabetic coma from coma due to any of these conditions depends on the blood sugar. A marked hyperglycemia with or without marked glycosuria is found only in diabetic coma while the other conditions enumerated in the foregoing present only a slight rise of the blood sugar, or none at all. In uremic coma the blood urea is high, and it is thus a wise procedure in all cases of coma to estimate the blood urea in addition to the blood sugar, the acetone and the carbon dioxide. Moreover, even in a case of undoubted diabetic coma these examinations are of value as they throw light on the functional activity of the kidneys, and thus aid in indicating the prognosis.

## INCIDENCE OF SYPHILIS IN DIABETES

Syphilis is a complication that is infrequently associated with diabetes. It is occasionally encountered, however, for a patient with diabetes is not immune to other infections. In this series of my own cases syphilis has been present in 2.6 per cent. A search of the literature shows that the majority of observers place the incidence of syphilitic infection

TABLE 15—*Blood Sugar Changes Following Intravenous Administration of Glucose (From Author's Study of One Thousand Cases of Diabetes)*

Case	Blood Sugar Content and Time	10 per Cent Dextrose, Cc	Blood Sugar Readings and Time
1	810 (3 35 p m)	250	706 (4 00 p m)
	612 (3 00 p m)	250	606 (4 15 p m)
2	123 (8 30 a m)	250	114 (11 30 a m)
	158 (9 00 a m)	250	182 (2 00 p m)
3	210 (10 30 a m)	250	187 (3 45 p m)
	216 (10 25 a m)	500	194 (3 20 p m)
	204 (3 30 p m)	500	191 (5 00 p m)
4	277 (10 00 a m)	500	238 (12 10 p m)
5	554 (11 00 a m)	250	323 (7 30 p m)
	300 (9 00 a m)	125	145 (5 00 p m)
6	109 (12 00 m)	250	263 (2 00 p m), 160 (4 00 p m), 111 (6 00 p m)
	46 (12 00 m)	125	37 (2 00 p m), 38 (4 20 p m)
	38 (4 30 p m)	250	103 (7 30 p m)
	71 (10 30 a m)	250	137 (1 30 p m), 157 (4 30 p m)
7	467 (3 51 p m)	250	410 (5 50 p m)
	423 (10 18 a m)	2 0	497 (11 30 a m), 348 (12 37 p m)
	343 (12 37 p m)	250	330 (1 30 p m), 300 (2 30 p m), 316 (3 30 p m)
	316 (3 30 p m)	250	309 (4 30 p m), 250 (5 30 p m), 282 (6 30 p m)
	344 (9 00 a m)	250	389 (11 00 a m), 348 (1 00 p m), 294 (3 00 p m)
	294 (3 00 p m)	250	300 (5 00 p m), 248 (7 00 p m)
	563 (12 00 m)	250	497 (2 00 p m), 475 (4 00 p m)
	475 (4 00 p m)	250	410 (6 20 p m)
	475 (11 00 a m)	250	370 (1 00 p m), 243 (3 00 p m), 116 (5 00 p m)
	116 (5 00 p m)	250	50 (7 00 p m)
	389 (11 00 a m)	250	300 (1 00 p m), 272 (5 00 p m)
	428 (11 00 a m)	250	336 (2 00 p m), 258 (5 00 p m)
	258 (5 00 p m)	250	208 (7 00 p m)
	309 (11 30 a m)	2 0	240 (2 00 p m), 171 (3 30 p m)
	171 (3 30 p m)	250	171 (5 00 p m), 134 (7 01 p m)
	410 (11 00 a m)	250	375 (2 00 p m), 252 (5 35 p m)
	535 (8 30 a m)	250	416 (11 00 a m)
8	256 (9 25 a m)	250	316 (11 00 a m)
	316 (11 00 a m)	250	352 (1 00 p m)
	352 (1 00 p m)	250	120 (7 25 p m)
	416 (11 30 a m)	250	344 (2 00 p m), 114 (4 35 p m)
	114 (4 35 p m)	250	53 (7 00 p m)
	172 (10 35 a m)	250	176 (12 30 p m), 85 (2 30 p m), 63 (4 30 p m), 67 (6 30 p m)

associated with diabetes between 2 and 3 per cent. Joslin<sup>3</sup> found 1.7 per cent in a series of 3,200 cases. Rosenbloom,<sup>4</sup> on the other hand, found syphilis to be present in 11 per cent of a series of 139 cases (table 16).

Warthin and Wilson<sup>5</sup> state that within the last nine years in the necropsy service of the pathologic laboratory at the University of Michigan there have been six necropsies in cases of diabetes mellitus all

<sup>3</sup> Joslin (footnote 1) pp 586, 605

<sup>4</sup> Rosenbloom, J, cited by Joslin (footnote 1, p 611)

<sup>5</sup> Warthin, A S, and Wilson, U F. Am J M Sc **152** 157-164 (Aug) 1916

of which showed histologic changes characteristic of syphilis, and that in four of these spirochetes were demonstrated in the myocardium and in one in the pancreatic lesions also

#### DIABETIC SURGERY

A number of years ago Foster<sup>6</sup> looked up the mortality statistics of operations on diabetic patients in several hospitals, and on averaging them, found that in 45 per cent infection developed, this high figure demonstrating a lowered resistance. According to him, these patients also have a low recuperative power and the tissue repair is sluggish, these being the principal factors responsible for the high mortality rate. Joslin<sup>7</sup> has pointed out the high incidence of diabetes among obese persons. A fat diabetic patient, on the other hand, as pointed out by Foster,<sup>6</sup> indicates a mild stage of the disease, which, however, will become severe in time if the patient is untreated. If an obese diabetic

TABLE 16—*Incidence of Syphilis in Diabetes (Compiled from the Literature)*

Author	Number of Cases of Diabetes	Number of Cases of Syphilis	Incidence, per Cent
Joslin (The Treatment of Diabetes Mellitus, pp 586, 605)	3,200	55	1.7
John	1,000	26	2.6
Williams (cited by Joslin, p 605)	143	4	2.7
Rosenbloom (cited by Joslin, footnote 1, p 611)	139	16	11.0
Smith (Virginia M. Month 49 662, 1923)	79	2	2.5
Fitz and Murphy (cited by Joslin, p 140)	50	5	10.0
Von Saun (Joslin, p 606)	12	1	1.3
Hirschfeld (cited by Rosenbloom J A M A 68 1232, 1917)			6.0

patient starts vomiting after an operation, he is in greater danger of acidosis than a patient who is underweight, and he will thus require the intravenous administration of glucose and insulin in order to combat the acidosis.

Infection in a diabetic patient diminishes the ability of the patient to utilize carbohydrates, and therefore the blood sugar content increases, this in turn causes an incomplete combustion of fat, with the appearance of ketone bodies in the blood and in the urine, and acidosis develops early and quickly. Increase of temperature also causes an increased metabolism, which in turn contributes to the production of acidosis. If present, nausea and vomiting automatically limit the fluid intake, a condition which in itself alone aggravates the acidosis and is likely to precipitate coma, owing to the fact that since the intake of food is inadequate the body tissues are drawn on for the increased demands of protein for energy. In consequence, there is increased protein catabolism, which is evidenced by the elevated urinary nitrogen, and the fat

<sup>6</sup> Foster, N. B. Surgical Aspects of Diabetes, J A M A 84 572-576 (Feb 21) 1925

<sup>7</sup> Joslin (footnote 1) p 140

catabolism is increased, especially in obese persons. It is for this reason that the intravenous administration of glucose together with insulin in cases in which there is vomiting is an efficient medical measure.

The effects of anesthesia in a diabetic patient do not differ in kind from the effects in other patients, but they are more pronounced. Ether anesthesia increases the blood sugar. In one of my cases, that of a boy, aged 5 years, a tonsillectomy was performed under ether anesthesia which lasted for fifteen minutes. The blood sugar before the administration of the anesthetic was 303 mg per hundred cubic centimeters, immediately after the operation it was 434 mg per hundred cubic centimeters, but there was no change in the carbon dioxide content of the blood nor in the plasma acetone. In one of my diabetic cases, after the removal of a cyst from the breast under ether anesthesia the blood sugar rose from 122 to 303 mg per hundred cubic centimeters, the plasma acetone to 2 plus, the plasma carbon dioxide to 42.4 per cent by volume, and there were marked clinical signs of acidosis.

Dewes<sup>8</sup> ascribes the slight increase in the glycemia which occurs during local anesthesia for extraperitoneal operations entirely to the anesthetic. The increase in the glycemia is much greater in laparotomies than in other operations, sometimes amounting to from two to four times the normal figure.

Pemberton and Cunningham<sup>9</sup> also report that ether anesthesia in a diabetic patient produces a more severe hyperglycemia and a greater fall in the alkali reserve than in a nondiabetic patient, but that this can be controlled by the use of insulin. In spite of the use of insulin, however, the postoperative sepsis appears to produce both hyperglycemia and a low alkali reserve, although the latter complication can be corrected by alkali therapy.

Seitz<sup>10</sup> studied the blood sugar in cases of exophthalmic goiter and found a high hyperglycemia, which he thinks is probably due to the increased irritation of the sympathetic system. He found that fourteen days after operation the sugar metabolism and the tonus of the involuntary nervous system had become normal. He made the remarkable observation that after strumectomy in some cases of diffuse colloid goiter, the alimentary hyperglycemia and the sympathetic tonus were increased.

Tables 17 and 18 show the general mortality in my series of 1,000 cases of diabetes to be 6.2 per cent, with an operative mortality of 20 per cent. Four of the patients who died, however, should properly be excluded from this list. In case 3, in which erysipelas developed,

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8 Dewes, H. *Arch f klin Chir* **122** 173-187, 1922.

9 Pemberton, H. S., and Cunningham, L. *Lancet* **2** 647-648 (Sept. 27) 1924.

10 Seitz, E. *Mitt a d Grenzgeb d Med u Chir* **34** 514-526, 1922.

death occurred from this cause. In case 4, only an exploratory operation was performed, a general carcinomatosis being discovered, no further operation was performed, and the patient died a few months later. In case 6, in which a leg was amputated, gangrene developed in the other leg, the patient dying from the infection without surgical intervention. In case 7 death was not the result of the operation but of the extreme severity of the diabetes, the patient being markedly emaciated and

TABLE 17—*Operative Mortality in Diabetic Patients (From Author's Study of One Thousand Cases of Diabetes)*

Total number of diabetic cases	1,000
Died (various causes)	62
Mortality, per cent	6.2
Diabetic patients operated on	35
Operative mortality	7
Mortality, per cent	20
Corrected mortality, per cent	8.5

Type of Operation	Age	Cause of Death
Thyroidectomy	67	Myocardial failure
Thyroidectomy	43	Myocardial failure
Mastoid*	48	Erysipelas
Cancer of liver* (exploratory operation)	58	General carcinomatosis
Thyroidectomy	72	Cardiac failure
Amputation of leg*	61	Gangrene of other leg
Abscess of lung*	58	Emaciation and exhaustion

\* Excluded from "corrected mortality" for reasons stated in text

TABLE 18—*Operations Performed on Diabetic Patients in the Cleveland Clinic Hospital (From Author's Study of One Thousand Cases of Diabetes)*

Operations	Number of Cases	Died
Thyroidectomy	12	4
Amputation of leg	10	1
Resection of rib	2	1
Prostatectomy	2	
Cholecystectomy	1	
Resection of breast for tumor	1	
Laparotomy	2	1 (general carcinomatosis)
Tonsillectomy	3	
Resection of cecum for carcinoma	1	
Mastoidectomy	1	

exhausted. If, then, these four cases are excluded, the operative mortality becomes 8.5 per cent. It will be further noted from the table that the remaining deaths were all in cases of hyperthyroidism, which seems to be especially hazardous in the presence of diabetes. It appears that with the use of compound solution of iodine (Lugol's solution) this danger will be eliminated. Joslin<sup>11</sup> reports that in the fourteen operations by F. H. Lahey on Joslin's diabetic patients for disease of the thyroid gland there was but one death.

A general summary of operative mortality in diabetic cases as reported in the literature is given in table 19.

<sup>11</sup> Joslin (footnote 1) p. 629

PREOPERATIVE AND POSTOPERATIVE TREATMENT OF PATIENTS  
WITH DIABETES

After an operation on a diabetic patient the first forty-eight hours is the crucial period which determines the outcome. During that period it is essential that the internist direct the treatment, and that he be thoroughly informed regarding the progress of the patient, not daily but hourly. The anticipation and prevention of postoperative complications is the essential feature of successful postoperative treatment.

It is of especial importance that vomiting be prevented. By the use of nitrous oxide oxygen anesthesia or local anesthesia this is almost eliminated. If orange juice and coffee with sugar is given to the patient

TABLE 19—*Operative Mortality in Diabetic Cases (Compiled from the Literature)*

Author	Year	Number of Operations	Mortality, per Cent
Morrison (Boston M & S J 175 51, 1916)	1896-1913	775	23
Karewski (Deutsche med Wchnschr 40 8, 1914)	1914	68	11.8
Berkman (Journal Lancet 36 309, 1916)	1915	26	7.6
Strouse (M Clin Chicago 2 37, 1916)	1916	38	31
Joslin (The Treatment of Diabetes Mellitus, p 626)	Before 1917	27	18
	1919	61	9
Fitz (M Clin N Amer 3 1107, 1920)	1918	45	30
Mugind, H	1921	5	80
Weeden (J A M A 82 1163, 1924)	1897-1922	160	36.8
		12	16.6*
Binney	1916-1923	32	19
Jones (Boston M & S J 188 483, 1923)	1923	8	25
Young (Boston M & S J 188 767, 1923)	1918-1922	99	16.1
Adams and Wilder (Wisconsin M J 22 557, 1924)	1924	327	1.2
Lahey		14	7.1†
Foster N B (J A M A 84 572, 1925)	1925		45‡
John	1921-1925	35	20
Corrected mortality			8.5

\* Insulin cases

† Thyroid

‡ Statistical report from several hospitals

early on the morning of the operation, it will help to prevent acidosis, with the resultant nausea and vomiting. It is also a good routine procedure to give the patient, as soon as he is off the operating table, an intravenous infusion of 250 cc of 10 per cent glucose solution to which has been added 10 units of insulin. It is important that this solution should be made with freshly distilled water to prevent reactions. This infusion is an excellent preventive measure against acidosis, it supplies both food and liquid to the body, and the insulin helps to burn up the carbohydrate and incidentally the acid bodies which may be present in the blood. With a good start thus induced, the further progress of the patient will usually take care of itself. The glucose can be repeated if indications for it exist. It is a good plan when giving glucose to precede the injection by the withdrawal of about 8 cc of blood for examination for sugar, acetone and carbon dioxide, as the information thus secured gives definite information as to the patient's status. I always administer insulin intravenously so that at the time each dose is given I can secure

a specimen of blood through the same puncture, and can thus follow every phase in the progress of the case from day to day, or more frequently if necessary. One cannot have too many data on a case, for too few data may be misleading. It does no harm to withdraw from 2 to 5 cc of blood daily, or several times a day for the first three or four days.

The postoperative course of patients treated according to the routine outlined in the foregoing has been uneventful. However, no measure is of avail if a patient has a septicemia from gangrene or from an infected gallbladder. Thus, a blood culture will be of great help in judging the prognosis in any given case.

It is important that the patient should receive abundant liquids. If for any reason they cannot be taken by mouth or by rectum, hypodermoclysis should be instituted immediately and kept up until the patient is able to take sufficient fluid by mouth.

The use of insulin has also been of great aid in the control of other than diabetic operative cases. I believe it is a good routine measure to use it in small doses in any operative case as long as the patient is in the hospital, whether or not it is indicated by the blood sugar estimations. It should be borne in mind that certain cases are functional cases of diabetes. This, however, cannot always be determined with certainty, as it often takes weeks or months to establish the status. In cases of functional diabetes there is a good chance that the islands of Langerhans may be restored, provided a properly balanced diet is given, but the restoration may be hastened by the addition of insulin. Insulin is of little, if any, value in the anatomic type of diabetes in which fibrosis of the islands of Langerhans is present, but it also can do no harm in such cases. Thus, as long as we do not know with which type of case we may be dealing, or whether or not any given case may be a potential case of diabetes—since in many operative cases the pancreas must share in the general debility of all the organs and tissues—we can play safe by using insulin.

To illustrate a typical record in an operative diabetic case, I offer one of many similar records in chart 7.

A man, aged 62, in childhood had had measles and mumps, later, rheumatism and erysipelas. He came to the Cleveland Clinic, June 7, 1924, because his toe was turning black. On May 30, he had noticed a slight abrasion on his toe. He had applied iodine but the toe began to swell, and in forty-eight hours it began to become discolored. The man did not know that he had diabetes, as he had apparently been in perfect health up to that time, he had lost only 10 pounds (4.5 Kg) in weight, and had not been a heavy eater. When he came to the clinic, his blood sugar content was 222 mg per hundred cubic centimeters, and glycosuria was present, the Wassermann reaction was negative. He was placed in the diabetic hospital of the Cleveland Clinic on routine diabetic treatment, and ten days later, as the gangrene was beginning to spread, the right leg was amputated below the knee. In thirty-two days he

was discharged from the hospital. The stump had completely healed, the blood sugar content was normal, and it was not considered necessary for him to take insulin. Subsequent blood sugar examinations gave a normal result even after his diet was increased.

This patient apparently had a mild case of diabetes with a senile type of arteriosclerosis, which had as much to do with the production of the gangrenous condition as did the diabetes.

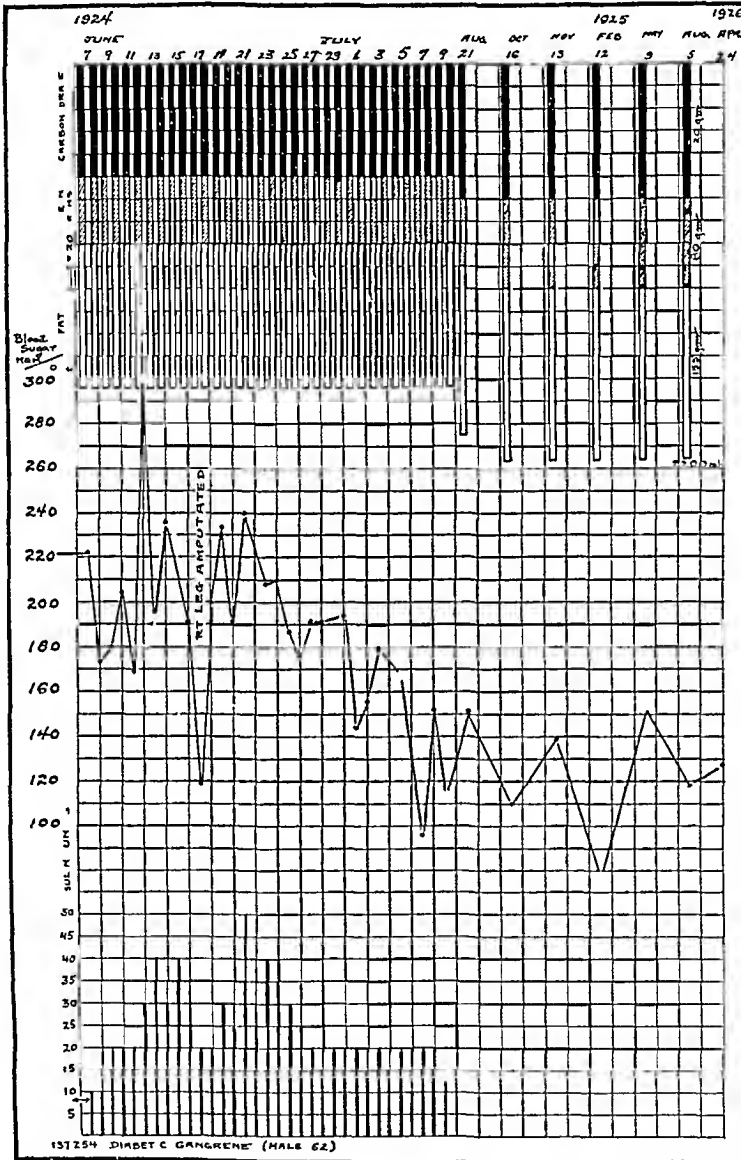


Chart 7—A typical chart illustrating the progress of a diabetic patient after operation

#### DISCOVERY OF DIABETES DURING EXAMINATION FOR LIFE INSURANCE

That in many cases the first indication of a diabetic condition is disclosed by an examination for life insurance is generally recognized. In 39 per cent of this series the condition was thus discovered, and this

is a lower percentage than is given in Joslin's<sup>12</sup> review of the literature on this point (table 20). Examinations for life insurance are thus of considerable value in this connection, for most of the patients in whom diabetes was thus discovered would not have sought medical aid at that time. The condition would have been discovered eventually, but not until the general physical condition had been weakened and the pancreatic function more seriously injured, the gravity of the prognosis being proportionately increased.

## SUMMARY

The incidence of diabetes among all diseases seen at the Cleveland Clinic during the period covered by this report on a series of 1,000 cases has been 1.8 per cent.

The percentages of males and of females in the series are practically equal.

TABLE 20—*Increasing Frequency of Discovery of Diabetes During Examinations for Life Insurance*

Period	Number of Cases	Sex		Discovered by Life Insurance		
		Male	Female	Total, per Cent	Male, per Cent	Female, per Cent
After Joslin, 1893-1916	1,000	594	406	6	10	0
1916-1920	1,000	578	422	9	15	1
1920-1923	1,000	524	476	13	22	2
Author's series, 1921-1925	1,000	466	534	3.9	2.9	1

The largest incidence of diabetes as shown by this series is in the sixth and seventh age decades.

The incidence of syphilis in this series was 2.6 per cent.

There was an hereditary history of diabetes in 4.6 per cent of these cases, a familial history in 5.1 per cent.

Diabetes was found through an examination for life insurance in 3.9 per cent of the cases.

The highest blood sugar level on admission was 908 mg. per hundred cubic centimeters in the case of a middle-aged man who has recovered sufficiently to carry on his occupation. Blood sugar figures as high as 310 mg. per hundred cubic centimeters were encountered without glycosuria. The diabetic renal threshold was high in many cases.

The general belief that insulin once used must always be continued is shown to be fallacious by the tabulation of cases in which good progress has followed the discontinuance of insulin.

The mortality rate in thirty-five operations on diabetic patients in this series was 20 per cent. By the exclusion of four cases in which

<sup>12</sup> Joslin (footnote 1) p. 122

death was due to septicemia, which was present at the time of the operation, or to inoperable carcinoma, the mortality rate is reduced to 8.5 per cent

Insulin reactions were not due to hypoglycemia in nearly 50 per cent of my cases, in fact, actual hyperglycemia was demonstrated. In the comment on the time relation of the insulin reaction to the dosage of insulin and to the blood sugar level it has been shown that there is marked irregularity in the factors that are supposed to play a part in the production of this reaction.

In the twenty-eight cases of diabetic coma discussed, fourteen patients were under observation at the Cleveland Clinic. Among these fourteen, seven survived and seven died, the latter being brought to the hospital in extremis and dying in from one to a few hours after admission. In the other fourteen cases, the patients had been discharged from my service and were living outside the city when coma developed as the result of some intercurrent infection, all these fourteen patients died.

The blood sugar in the cases of coma at the clinic ranged from 200 to 810 mg per hundred cubic centimeters, the plasma acetone from 0 to 3 plus, and the plasma carbon dioxide from 44.3 to 99 mm of pressure. The higher figures in the last instance were due to the administration of insulin previous to the carbon dioxide determination.

# DIET DETERMINATIONS

## A GRAPHIC METHOD <sup>\*</sup>

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A graphic method of determining the protein, fat and carbohydrate constituents of a diet, without calculation, is presented in this article. The method is adapted for use with diets of any caloric content up to 5,000 calories and for a range of fat-carbohydrate ratios from 1:2 up to 4:1. A chart of this type, that is equally serviceable for a large variety of dietary requirements, has not, so far as we are aware, appeared in the previous literature.

The triangular diagram of the type used by Du Bois <sup>1</sup> is of equally general application, this gives protein, fat and carbohydrate in percentages, however, and correlates them with the respiratory quotient, it is therefore less convenient for use when total caloric intake and fat-carbohydrate ratio are two of the arbitrarily fixed constants in the determinations.

For the determination of diets in diabetes, two nomographic charts have been published, that of Hannon and McCann,<sup>2</sup> and that of Wilder.<sup>3</sup> The former, which is an ordinary Cartesian diagram, is based on the Woodyatt<sup>4</sup>  $FA/G$  ratio, in which its value is 1.5, and diets can be determined by it for this value of the ratio only. The elements of the Woodyatt  $FA/G$  ratio, as is well known, are calculated from the following formulas:  $G = C + 0.58 P + 0.1 F$ , and  $FA = 0.46 P + 0.9 F$ . With this, and the formula for total calories ( $M = 4.1 C + 4.1 P + 9.3 F$ ), the Hannon and McCann type of chart can be constructed.

Wilder's chart is an alignment diagram, also limited to a single fat-carbohydrate ratio. It is based on a simplification of the Woodyatt formula. Wilder assumed that in 100 Gm of protein there were 58 Gm of carbohydrate, 16 Gm of nitrogen and 26 Gm of material

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<sup>\*</sup> From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York City.

1 Du Bois, E. F. Basal Metabolism in Health and Disease, Philadelphia, Lea and Febiger, 1924.

2 Hannon, R. R., and McCann, W. S. Bull. Johns Hopkins Hosp. **33**: 128 (April) 1922.

3 Wilder, R. M. Optimal Food Mixtures for Diabetic Patients, J. A. M. A. **78**: 1878 (June 17) 1922.

4 Woodyatt, R. T. Objects and Method of Diet Adjustment in Diabetes, Arch. Int. Med. **28**: 125 (Aug.) 1921.

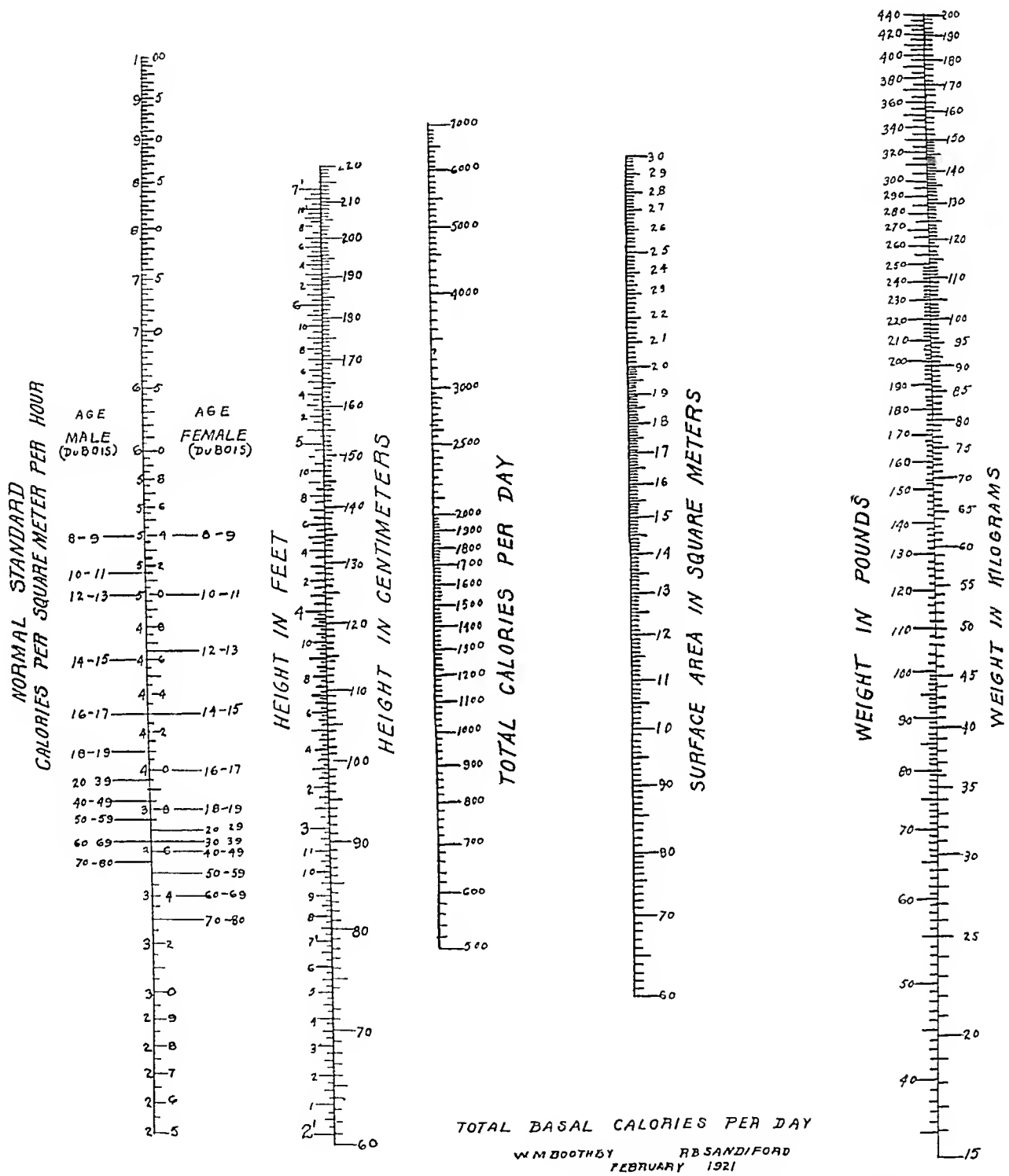


Chart 1—Boothby and Sandiford's chart for the determination of basal food calory requirements

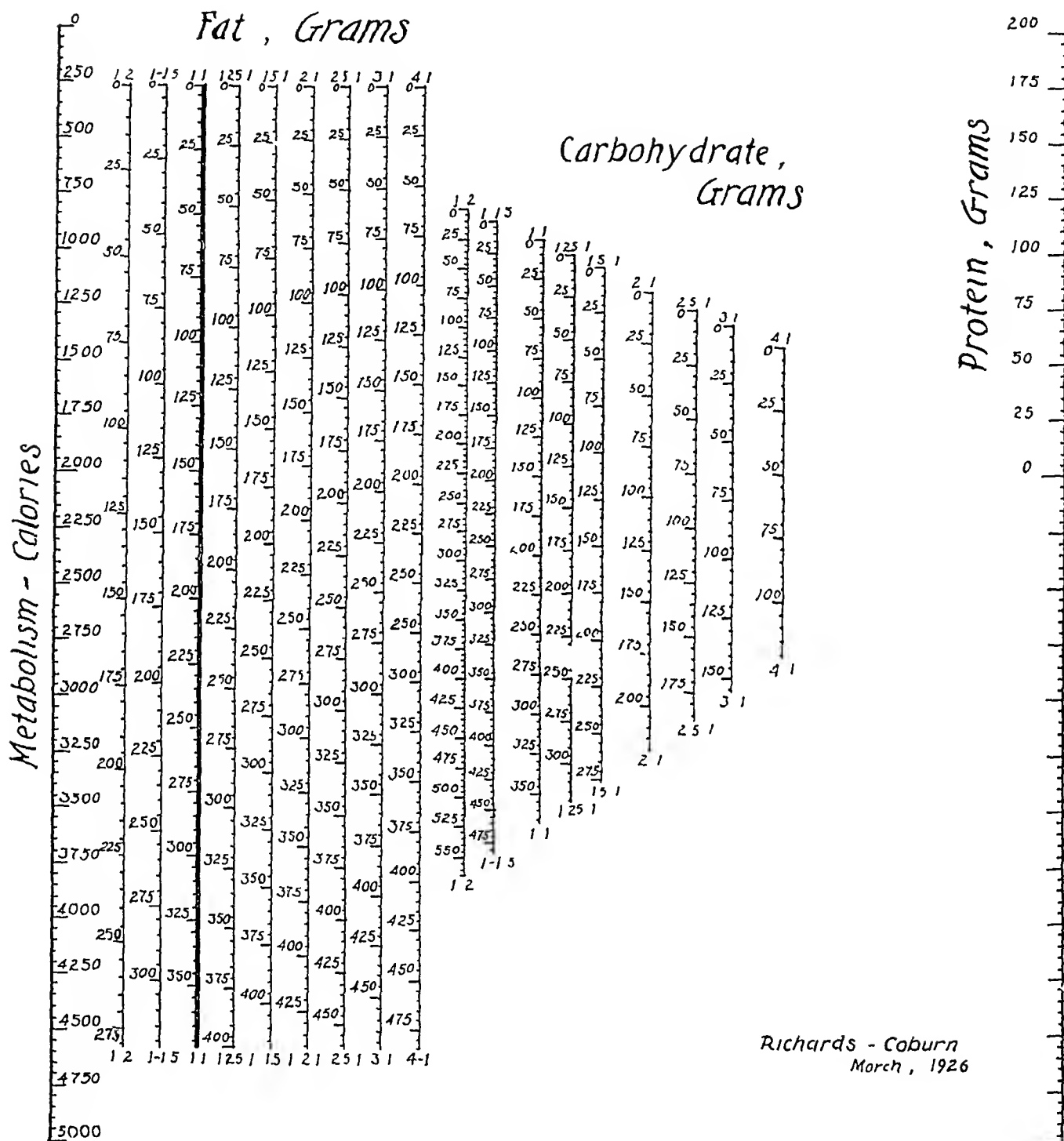


Chart 2—Chart for determination of fat, carbohydrate and protein constituents of diets (a) first scale, total calories, (b) next eight scales, grams of fat for eight different fat-carbohydrate ratios, (c) next eight scales, grams of carbohydrate for eight different fat-carbohydrate ratios, (d) last scale (right side of chart), grams of protein

"either ketolytic or neutral" Calculating them all as ketolytic, in the form of aceto-acetic acid, he found that 23 Gm of glucose would be needed for their combustion By disregarding the glycerol fraction of the fat, Wilder's  $FA/G$  ratio then simplified to  $\frac{FA}{G}$

To this  $FA/G$  ratio, Wilder assigned the value of 4

For our  $FA/G$  or  $R$  values we have used the simple relationship  $R = \frac{F}{C + \frac{(0.58 - 0.23)P}{0.58}}$  as used by Palmer and Ladd<sup>5</sup> in their work on ketogenesis in diabetic patients This has not all the theoretical accuracy of the Woodyatt or Shaffer<sup>6</sup> formulas, but is probably well within the general accuracy of calculation of diets by ordinary quantitative methods

This formula gives, of course, appreciable differences in  $R$  values as compared with those given by the other formulas, but for most diets these differences will not be more than 0.2 or 0.3 Maximum differences would occur when  $P$  is large and  $C$  small and  $F$  either very large or very small If  $F = 50$ , for example,  $C = 50$ ,  $P = 100$ , then  $R$  by the Wilder formula would be  $\frac{1}{1.7}$ , and by the Palmer-Ladd ratio which we have used,  $R = \frac{1}{2.2}$

#### CONSTRUCTION

The chart is a D'Ocagne nomogram, constructed in the same manner as Wilder's chart The method has been described by Wilder, Henderson<sup>7</sup> and others in recent literature and will not be reviewed here The basic formulas used are

1 Ratio (Palmer-Ladd)  $= \frac{\text{Gm } F}{\text{Gm } C + \frac{0.58}{0.58} \times \text{Gm } P}$  in which available carbohydrate  $= (\text{Gm carbohydrate}) + (0.58 \text{ Gm protein})$ , and fat  $= 100$  per cent  $F$

2 Total calories  $= (9.3 \times \text{Gm } F) + (4.1 \times \text{Gm } C) + (4.1 \times \text{Gm } P)$

Because of the mechanics of construction, values for carbohydrate requirements fall on discrete parallel vertical lines for each fat-carbohydrate ratio, and values for fat requirements fall on one vertical line for all ratios As this difficulty defeats the purpose of the chart, an expedient is taken The values of fat requirements for each ratio are transposed horizontally (from the points where they fall) to a parallel line drawn in at an arbitrary distance

The average error in determining a diet by the use of this chart is not more than 2 Gm of any constituent and less than 20 calories of the total calory scale The accuracy is well within that obtainable by ordinary quantitative measurements of food substances

<sup>5</sup> Ladd, W. S., and Palmer, W. W. Proc Soc Exper Biol & Med **18** 109, 1920, Am J M Sc **166** 157 (Aug) 1923

<sup>6</sup> Shaffer, P. A. J Biol Chem **54** 399 (Oct) 1922

<sup>7</sup> Henderson, L. J. J Biol Chem **59** 379 (March) 1924

As will be seen, the chart can be used for almost all types of diet, as the fat-carbohydrate ratios range in value from 1.2 up to 4.1

The complete system presented consists, as did that of Wilde<sup>8</sup> of two charts, the well known Boothby-Sandiford<sup>8</sup> chart for basal metabolic rate determinations (reprinted here by permission of the authors), and the one discussed above

From the former (knowing weight, height, age and sex), twenty-four hour caloric requirements are determined as follows

- 1 Locate weight and height points on their respective lines
- 2 Connect these with straight edge thus determining surface area
- 3 Locate point on "normal standard" line
- 4 Connect "normal standard" and surface area points with straight edge
- 5 Straight edge then crosses calory scale at basal twenty four hours' requirement

To use the diet chart, the caloric requirement (basal, or basal + 50 per cent, etc.) must be known, and one of the food elements must be arbitrarily fixed. This will ordinarily be the protein value, for example 1 Gm per kilogram of body weight. A definite fat-carbohydrate ratio (*R*) must also be chosen.

With these values known, the fat and carbohydrate requirements are then read off as follows

- 1 Locate protein and caloric requirements on their respective lines
- 2 Connect these with straight edge
- 3 The carbohydrate requirement can then be read on the proper *R* line
- 4 The fat requirement can be read on heavy line for 1.1 ratio
- 5 For any other ratio, the fat requirement is determined by observing the point where the straight edge crosses the 1.1 (heavy line), and then with this point as a center rotating the straight edge to the horizontal position and reading on the proper *R* line the fat requirement. (It will be noted that the protein line has been extended downward and graduated similarly to the calory scale in order that the straight edge may be fixed at the horizontal without difficulty.)

This chart is also of service in determining changes of diet, 'isodynamic shifts,' etc

#### SUMMARY

For the determination of the protein, carbohydrate and fat constituents of a diet, without calculation, a graphic method is here presented. This can be used for many types of diet, and for a wide range of fat-carbohydrate ratios

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<sup>8</sup> Boothby, W. M., and Sandiford, R. B. Boston M. & S. J. 185:337 (Sept. 22) 1921

# FRAGILITAS OSSIUM AND DEAFNESS

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We report here four cases of blue sclerotics, brittle bones and deafness, three illustrate the symptoms and signs of the disease and one the familial transmission. The cases are characterized by blue sclerotics, early and continued occurrence of fracture, because of the fragile type of the bones, and sometimes the development in early youth of progressive deafness.

The disease is hereditary and a patient may have one, two or all symptoms. Children afflicted with the blue sclerotics alone usually die in infancy. When the blue sclerotics are first manifest in adolescence they are associated with brittle bones, and later deafness may supervene.

## HISTORY

Stobie,<sup>1</sup> in reviewing the literature, noted only twenty-seven cases or family groups—twenty-four from England and Germany and three from this country. Conlon<sup>2</sup> reported six cases in one family from Boston, Ostheimer<sup>3</sup> one case in a child of Russian Jew parentage from Philadelphia, and Herrman<sup>4</sup> one case from New York. We have been able to find reports of seven other families and cases in the American literature, most of these cases occurred east of the Alleghenies. Wise<sup>5</sup> presents a group of six cases from Baltimore, Van der Veer and Dickinson<sup>6</sup> two cases from Albany, Mixsell<sup>7</sup> one case from New York

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1 Stobie, William. The Association of Blue Sclerotics with Brittle Bones and Progressive Deafness, *Quart J Med* **17** 274-287 (April) 1924

2 Conlon, F A. Five Generations of Blue Sclerotics and Associated Osteoporosis, *Boston M & S J* **169** 16-19, 1913

3 Ostheimer, Maurice. *Fragilitas Ossium*, *J A M A* **63** 1996-1999 (Dec 5) 1914

4 Herrman, Charles. Blue Sclerotics Associated with Brittle Bones, Report of a Case in a Child Two Years Old, *Am J Dis Child* **9** 205-212, 1915

5 Wise, W D. *Fragilitas Ossium* with Blue Sclerotics, *J A M A* **73** 1696 (Nov 29) 1919

6 Vander Veer, E A, and Dickinson, A M. *Fragilitas Ossium*, *Ann Surg* **74** 629-632 (Nov) 1921

7 Mixsell, H R. Osteogenesis Imperfecta (Osteopathyrosis, *Fragilitas Ossium*), with Report of Two Cases, *Arch Pediat* **34** 756-764 (Oct) 1917

City, Goldbloom<sup>8</sup> one from Montreal, Rodriguez<sup>9</sup> one from Fort Wayne, Ind, Terry<sup>10</sup> two from San Francisco, and Flagstad, Zanger and Leven<sup>11</sup> two typical cases from St Paul. Two cases were observed in the Mayo Clinic in 1924, and three cases in 1925, the patients were from Wisconsin, Illinois and Missouri.

#### REPORT OF CASES

CASE 1—A man, aged 20, came to the clinic, Sept 6, 1924, complaining of pain in the back and the right hip. In June he had consulted a physician for palpitation of the heart. A blood test was said to be positive for syphilis and he was given an injection in the right gluteal region. Later two blood tests were negative. The injection caused severe pain for several days, then disappeared until August when it returned and interfered greatly with walking and

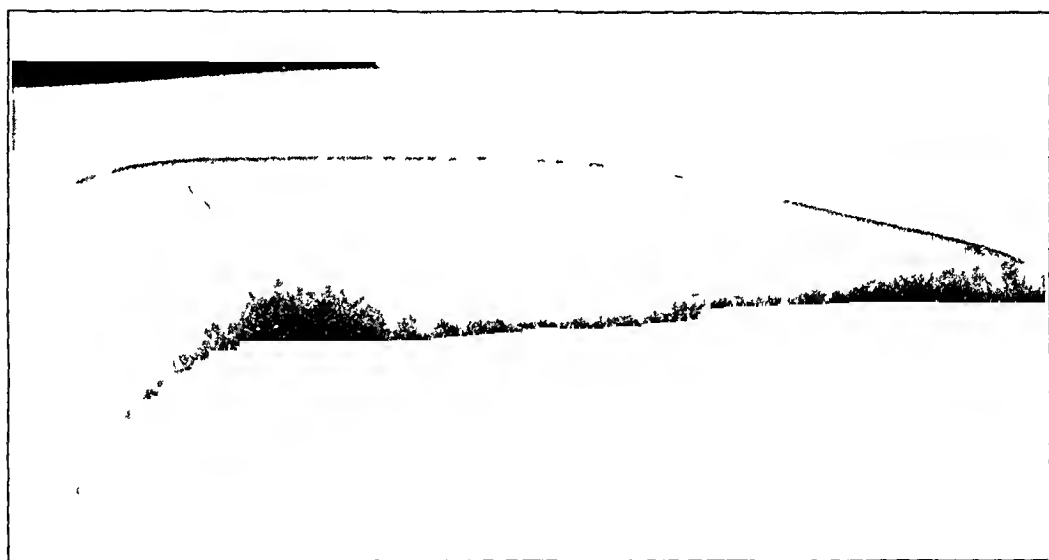


Fig 1—Myositis ossificans (case 1)

sleeping. There was a constant dull ache with sharper exacerbations when weight was placed on the right leg. Slight fever accompanied the pain.

At the age of 15 years the patient fractured an elbow by bumping it against a barn door. Later he fractured the other elbow by knocking it against the saddle while riding horseback. Two ribs were fractured by a kick of a horse. A rock fell on his leg and fractured the ankle. Two years later a fall from a wagon resulted in fracture of the collar-bone. He sprained his ankle on one occasion and his present trouble with his back appeared to be somewhat similar.

His mother said that his paternal grandfather, a German immigrant of Wisconsin, had had blue sclerotics. His father also had blue sclerotics, was deaf,

8 Goldbloom, Alton. Fragilitas Ossium, with Report of a Case, *Canad M A J* 7 636-640 (July) 1917.

9 Rodriguez, J. Idiopathic Osteopsathyrosis, *J Indiana State M A* 17 111-113 (April) 1924.

10 Terry, W I. Hereditary Osteopsathyrosis, *Ann Surg* 68 231-234 (Aug) 1918.

11 Flagstad, A E, Zanger, Elizabeth, and Leven, Logan. Blood Chemistry Study in Osteogenesis Imperfecta, Preliminary Report, *Minnesota Med* 7 800-804 (Dec) 1924.

and in his youth had had a fracture of the leg which failed to unite, the leg was finally amputated. The patient is one of nine children, six boys and three girls. Five of the family have blue sclerotics, one sister has had both arms and one leg broken, the other two sisters are deaf, and one brother has had a leg broken. Except for one brother in South Dakota, the family is living in Wisconsin.



Fig 2—Anterior view (case 2)

The patient's sclerotics were deep blue. When he entered the clinic he had a temperature of 102 F, which subsided within a few days. The leukocyte count was normal. Roentgenograms revealed hypertrophic arthritis and lateral curvature with rotation of the lumbar spine, areas of myositis ossificans in the muscles of the right thigh (fig 1), and ununited fractures of both elbows. It was believed that the pain in the back and hip was due to irritation of the nerve roots from rotation of the spine, and the patient was fitted with a short corset. The serum calcium was 8.5 mg, and the organic phosphorus 4.4 mg for each hundred cubic centimeters of blood.

CASE 2—A man, aged 47, came to the clinic, Oct 27, 1924, complaining of a gradually increasing pain in the right hip of twenty years' duration. He was 4 feet, 5.5 inches tall and weighed 108 pounds (49 Kg) (figs 2 and 3). When the patient was 2 years old, he fell off the bed and fractured his right arm. The same year he refractured it by a fall. Eight years later a snowball struck his right arm and fractured it in a different place, and within a year it was refractured three times by a thrown ball and slight injuries. At the same time



Fig 3—Lateral view of patient showing posture (case 2)

he fell off a horse and struck his head. As a result he carried his head to the left and had it immobilized for six weeks. When he was 12 years old a post fell on his thigh and broke his right femur. The next year he fell out of a buggy and broke his right collar-bone. When fourteen he jumped from a cart and broke his left femur. At the age of 27 he fell from a wagon and refractured his left femur. The patient has not grown since he was 10 years old. He has had deformities of head and legs as long as he can remember, but he was never aware of his blue sclerotics. Sexual power was normal in youth but has dimin-

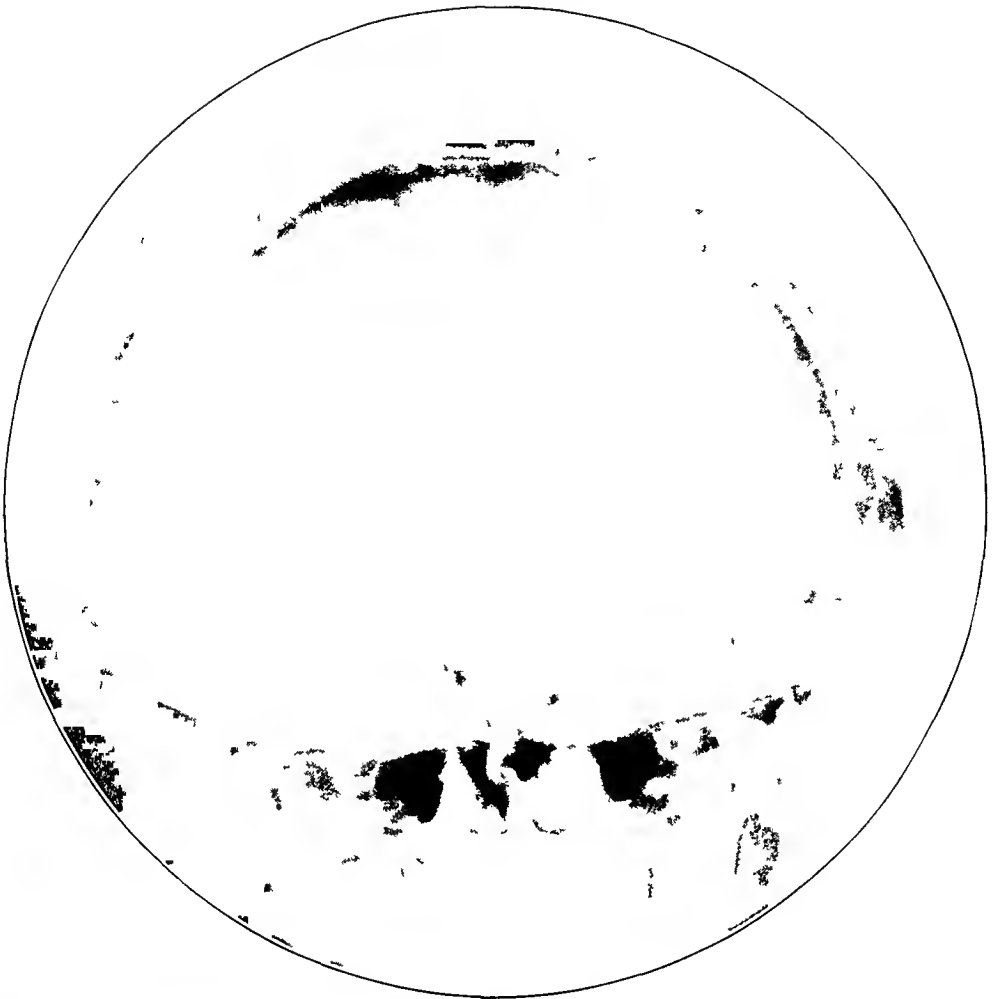


Fig 4—Head (case 2)



Fig 5—Head (case 2)

ished in the last twenty years. He has three brothers and four sisters, none of whom has blue sclerotics or brittle bones. Two brothers are deaf in one ear as a result of mastoidectomy.

The sclerotics were not as blue as in the first case, however, the color was distinctly deeper than normal. There was marked horizontal and vertical nystagmus, probably congenital. Roentgenograms (figs 4 and 5) revealed marked

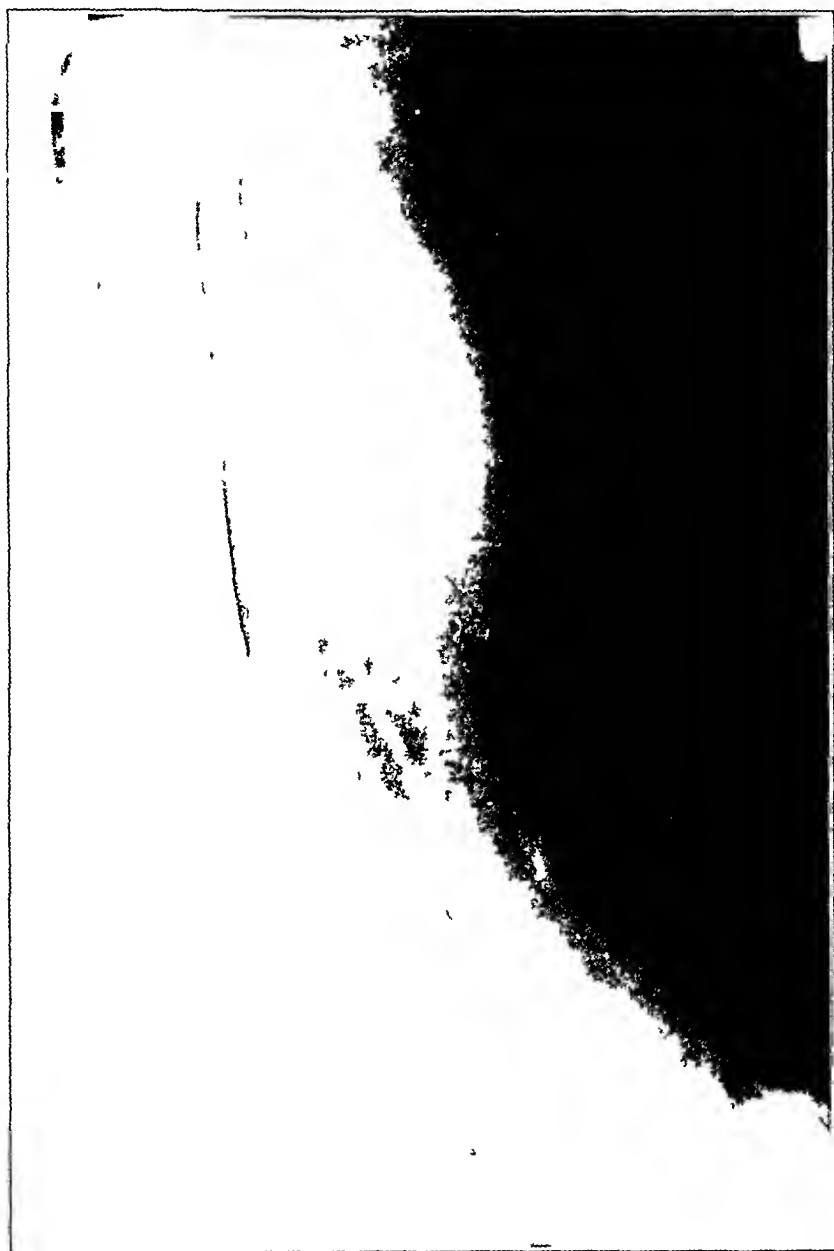


Fig 6—Bowling of bones of leg and sclerosis of posterior tibial artery (case 2)

bony deformity of the head, deformity of the pelvis with destructive arthritis of the right hip joint which accounted for the pain, bilateral rudimentary cervical ribs, slight arthritis of the hands, destruction of the body of the tenth dorsal vertebra, an old fracture of the lower third of the right humerus, and marked bowing of the tibiae and fibulae (fig 6). Certain of the long bones showed considerable atrophy. There was slight glycosuria with a fasting blood sugar of 110 mg for each hundred cubic centimeters. The serum calcium was 8.1 mg, and

the inorganic phosphorus was 46 mg for each hundred cubic centimeters of blood. Hearing was normal. Arteriosclerosis grade 3 was found.

CASE 3—A woman, aged 49, came to the clinic, Feb 29, 1925, complaining of nausea and vomiting, pain in the joints and severe headaches. The patient was the smallest of her family and had been aware of the blue sclerotics all her life. Deafness had been gradually increasing since her twentieth year. She said that her mother had been partially deaf in old age and that a sister was somewhat deaf. No one of her immediate family was especially susceptible to fractures. She had two nephews and a grandniece with blue sclerotics and the grandniece

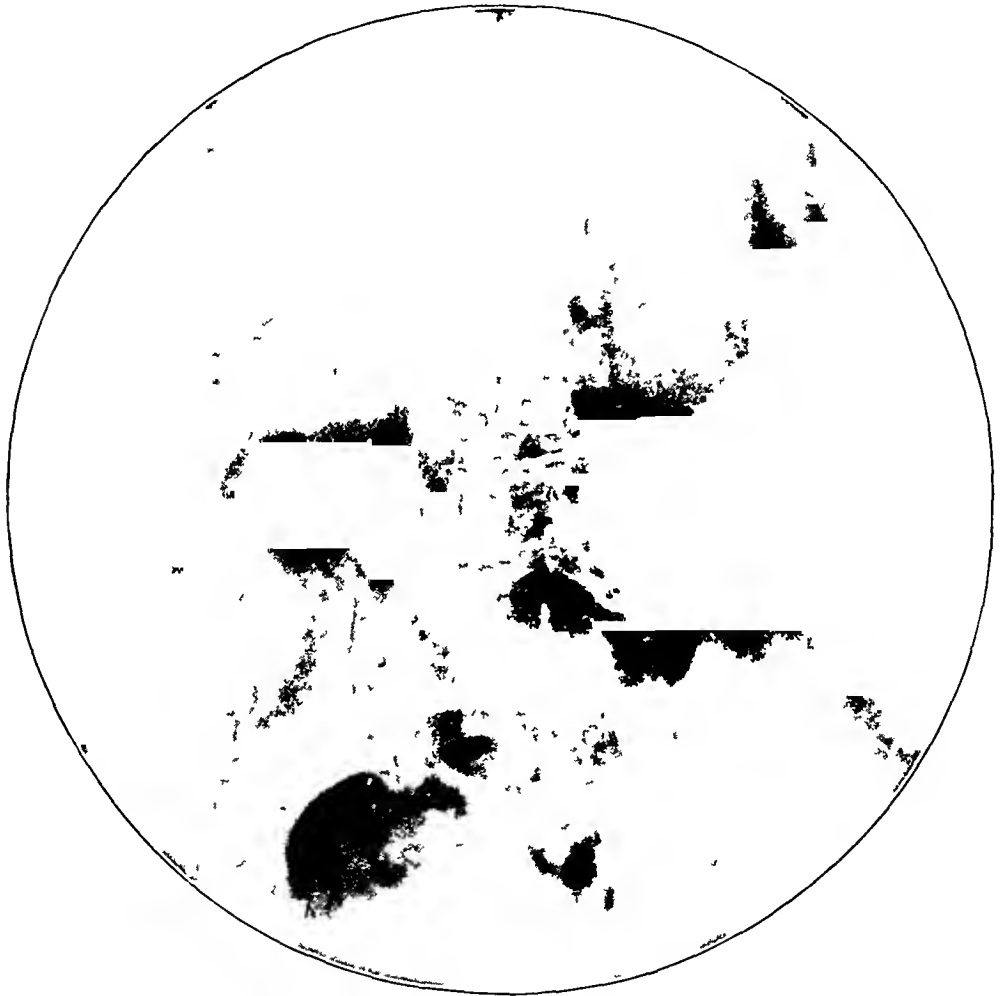


Fig 7—Pelvis (case 3)

also had brittle bones. A questionnaire sent to all branches of the patient's family gave the information that there were no blue sclerotics, brittle bones or deafness in the grandparents, parents, brothers or sisters or their children.

The patient was only 4 feet, 9 inches tall and weighed 70 pounds (31.8 Kg). She had marked generalized arteriosclerosis. The systolic blood pressure was 192 and the diastolic 118. The blood urea was 72 mg for each hundred cubic centimeters, and the phenolsuphonphthalein return was 30 per cent. The sclerotics were grayish blue with darker zones corresponding to the ciliary bodies, and there was a wide arcus senilis. The fundi showed moderate retinal arteriosclerosis of the hypertension type. There was advanced deafness of the nerve on both sides. Roentgenograms (fig 7) revealed considerable porosity of the bones of the extremities and marked atrophy of the bones of the spine and pelvis.

CASE 4—A woman, aged 52, came to the clinic because of a severe pain in her back. She also noticed that she was becoming shorter in stature. She presented the syndrome of blue sclerotics, brittle bones and progressive deafness. Her family history was traced through several generations and it was seen that she was a member of the third generation in which this syndrome had appeared. At present the members of the family are living in two states, Illinois and Oklahoma, but the ancestor in whom it first appeared lived in Waterford County, Ireland. The Irish grandmother had had blue sclerotics and suffered from frequent fractures, but was never deaf. Despite her disabilities she lived to the ripe old age of 95. She gave birth to three sons, one of whom inherited the blue sclerotics. One of the other two sons died at the age of 35, the other still living, has seven children, none of whom has blue sclerotics. The son with blue sclerotics was the father of eleven children, of whom the patient and five others inherited this characteristic. His oldest daughter has two children, one with, the other without it. The patient has five children, three with and two without the syndrome. The third child, a boy with blue sclerotics, is living and unmarried, the fourth son has two children, a boy with and a girl without blue sclerotics. The other two children with blue sclerotics died in infancy (fig 8).

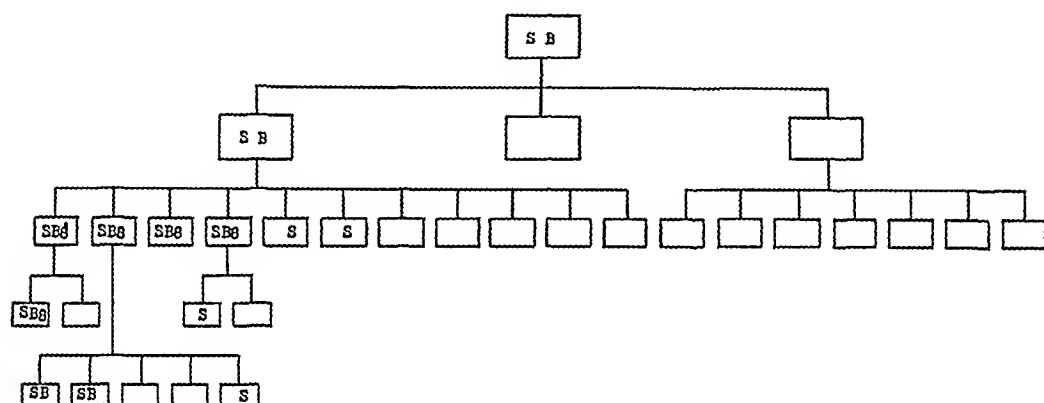


Fig 8—Family diagram (case 4) *S*, blue sclerotics, *B*, brittle bones, 8, nerve deafness, squares containing *S* alone indicate infants or those dying in infancy who had blue sclerotics but did not have time to develop indications of brittle bones by fractures

#### COMMENT

In all reported cases the color of the sclerotics was uniform. No matter in which direction the eyeball was turned the homogeneous leaden blue was seen through the scleral conjunctiva. The color was so distinct as to leave no doubt as to its significance. It is variously described as a porcelain or leaden blue, and appears to be due to an increased transparency of the sclerotics allowing the choroid to shine through, rather than to an extraordinary thinness. Bronson<sup>12</sup> has quoted six cases of the syndrome from the literature and added a seventh in which no hereditary tendencies were demonstrable. She notes that the sclerotics were not so blue in her patient as in the group from the literature.

The fractures may be spontaneous or associated with trauma. Roentgenograms have revealed atrophy of the bone. Patients are also said

<sup>12</sup> Bronson, E. On Fragilitas Ossium and Its Association with Blue Sclerotics and Otosclerosis, *Edinburg M J* 18 240-281 (April) 1917

to be susceptible to sprains. In case 2 the changes in the shape of the head with the flattening in both directions and the overhanging parietal bosses seems to be characteristic of the fragilitas ossium group. The relation of the deformity of the sella region, caused by the changes in the head, to the existing infantilism and glycosuria is an interesting subject for speculation. The type of infantilism apparent in this case resembles more closely that commonly called essential infantilism than the type that is the result of rickets, fragilitas ossium and similar bony changes, although manifestations of the latter type may also be included. The relation of the syndrome of blue sclerotics and brittle bones to the conditions known as fragilitas ossium, osteogenesis imperfecta and osteopsathyrosis is unknown. It is noteworthy that many authors of case reports of these diseases make no mention of color in the sclerotics nor of hereditary tendencies. For this reason some cases of blue sclerotics are probably included in these other groups. The accompanying deafness seems to be due to otosclerosis, a lesion of the auditory nerve.

The most plausible explanation for the cases of blue sclerotics with brittle bones and deafness is that they are caused by a congenital mesenchymal defect, since all the structures involved in the syndrome come originally from this anlage. However, this theory does not explain why other tissues of mesenchymal origin, such as the heart, blood and lymph vessels, bone marrow and lymph nodes, are not usually affected.

The third case is of unusual interest because of the associated cardiovascular degeneration. This degeneration, of course, may be coincidental but it also may be logically explained on the basis of an original defect in the mesenchyme. Very few cases of this syndrome have been reported in which there was involvement of the cardiovascular system. The atrophy of the bone was so great that had the patient led a more active life it is likely she would have had multiple fractures. The discrepancy between the patient's account of trouble similar to hers in other members of her family and the actual facts brought out by the questionnaires and the relatives shows that great care must be exercised in working out the family history in this type of case. Other associated defects, such as kyphosis, congenital heart disease, spina bifida and cleft palate, also occur.

Little is known of the metabolism of inorganic salts in these cases. Like Flagstad, Zangei and Leven, we have found normal values for serum calcium and inorganic phosphorus.

Case 4 is illustrative of the hereditary tendency of the syndrome. In this tree, all who lived beyond seventeen years had begun then, if at all, to show deafness, and the factor of brittle bones manifested itself in early childhood and throughout life in multiple fractures. It is interesting to note that approximately 50 per cent of the children of

each heir with blue sclerotics inherited the syndrome in whole or in part and in turn transmitted it. The other 50 per cent did not inherit and did not, in any part of their chain, manifest nor transmit a tendency to this syndrome. No definite sex linkage in transmissions nor immediate sequence was noticed in this particular family. The meaning of immediate sequence may best be illustrated by example, that is if we could foretell that a person with blue sclerotics would have four children, from our investigations we could not say how the 50 per cent tendency would follow, whether the first and fourth child, the second and third or the second and fourth in order of birth would have blue sclerotics and other manifestations of this syndrome. Neither does the presence of the syndrome seem to have any direct bearing on the longevity of the individual, for three members of this family have lived well over seventy-five years, the grandmother to 95.

In summing up the hereditary tendencies of this syndrome and its apparent 50 per cent transmission, we shall use the formula Guyer<sup>13</sup> sets forth in his book "Being Well-Born." He says, "In man as in lower forms some characters or traits are due presumably to the presence of determiners or their absence." He uses what he calls a "presence-absence" formula with the symbol  $A$  for the determiner and  $a$  for its absence. Thus  $AA$  represents a condition in which similar determiners have been derived from both parents and which is called duplex,  $Aa$ , a condition in which the determiner is from only one parent and hence simplex, and finally  $aa$ , in which there is total absence of determiner and which is called nullplex. From these pairs, six kinds of combinations are possible:

1	$aa \times aa$	$a-a$ $\times$ $a-a$	All nullplex
2	$aa \times Aa$	$a-A$ $\times$ $a-a$	50 per cent nullplex 50 per cent simplex
3	$aa \times A1$	$a-A$ $\times$ $a-1$	All simplex
4	$Aa \times Aa$	$A-A$ $\times$ $a-a$	25 per cent duplex 50 per cent simplex 25 per cent nullplex
5	$Aa \times AA$	$A-A$ $\times$ $a-A$	50 per cent duplex 50 per cent simplex
6	$AA \times AA$	$A-1$ $\times$ $A-A$	All duplex

In our case 4 we believe that the blue sclerotic is a simple dominant in the simplex form, and when united with a nulliplex as in formula 2, will produce offspring 50 per cent of whom show blue sclerotics. These, in their turn, will have an equal chance of transmitting blue sclerotics to 50 per cent of the next generation, and so on.

#### SUMMARY

In four cases with blue sclerotics, brittle bones and deafness presented, two are definitely hereditary while the other two reveal no familial tendency. The source of these groups seems to be from Europe. One of our cases definitely follows the mendelian law. The disease is uncommon. It is progressive although concomitant with longevity.

# THE MECHANISM OF PAIN IN GASTRIC AND IN DUODENAL ULCER

## III THE RÔLE OF PERISTALSIS AND SPASM

WALTER LINCOLN PALMER, M D  
CHICAGO

It has been shown that hydrochloric acid is an irritant that constitutes an adequate stimulus to the pain-producing mechanism of a sensitive ulcer. In this article data are reported regarding, first, the rôle of peristalsis and spasm in the distress so produced, and, second, the effect of peristalsis as a mechanical stimulus to the pain-producing mechanism. This evidence gives some information as to the relationship of the pain-producing mechanism to the ulcer.

### LITERATURE

In 1916, Ginsberg, Tumpowsky and Hamburger<sup>1</sup> reported the first experiments showing a muscle tension factor in ulcer pain. The following year Carlson<sup>2</sup> published some excellent kymographic tracings showing intermittent ulcer pain synchronous with gastric contractions, and concluded also that the pain was due, not to the acidity per se, but to the muscle tension. Hardt,<sup>3</sup> on the basis of similar work, drew the same conclusion a year later. In 1919 Homans<sup>4</sup> took exception to this view and contended that powerful, vigorous contractions of the fundus of the stomach might be present without pain and pain present without any contractions of the fundus. In 1922 Reynolds and McClure,<sup>5</sup> on the basis of their roentgenologic studies, concluded that there was no incontrovertible evidence of the relationship of ulcer pain to motor activity. Ortmayr<sup>6</sup> in 1925 confirmed Homan's work, and concluded that the pain of ulcer is not related to muscle tension but to the acidity

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1 Ginsberg, Harry, Tumpowsky, Isidor, and Hamburger, W. W. Contributions to the Physiology of the Stomach. XXXV. The Newer Interpretation of Gastric Pain in Chronic Ulcer, *J. A. M. A.* **67** 990 (Sept 30) 1916.

2 Carlson, A. J. Contributions to the Physiology of the Stomach. The Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, *Am. J. Physiol.* **45** 81 (Dec.) 1917.

3 Hardt, L. L. J. Pain in Active Pathologic Processes in Stomach or Duodenum, *J. A. M. A.* **70** 837 (March 23) 1918.

4 Homans, John. The Relation of Pain in Gastric and Duodenal Ulcer to Muscular Activity of the Stomach, *Am. J. M. Sc.* **157** 74 (Jan.) 1919.

5 Reynolds, L., and McClure, C. W. Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, *Arch. Int. Med.* **29** 1-11 (Jan.) 1922.

6 Ortmayr, Marie. Gastric Motor Activity in Patients with Peptic Ulcer, *Arch. Int. Med.* **35** 423 (April) 1925.

of the gastric content In 1921, Poulton<sup>7</sup> reported that the distress of gastric ulcer could be initiated by increasing gastric tension, and relieved by its reduction Hurst<sup>8</sup> ascribes the pain to muscle tension Ryle<sup>9</sup> states that "given an irritative focus, the ingestion of food, or the readiness for it, even in the absence of acid secretion, is an adequate stimulus for the initiation of the exaggerated tonic and peristaltic action upon which the pain depends"

#### METHODS OF STUDY

Previous investigators of the mechanism of ulcer pain were all handicapped by their inability to initiate and relieve the pain at will It was necessary to wait for spontaneous pain, which occurred at a time when the stomach contained food The sole exception was in Cailson's case, his patient evidently having an extremely sensitive pain mechanism The success of the acid injections altered the situation entirely and afforded a method for studying the stomach and duodenum before, during, and after the induction and relief of pain

Two main lines of investigation were followed in this study The first was the balloon method used by Cailson and others in the study of hunger contractions In this the patient swallows a small rubber condom, about 5 inches (12.7 cm) long, which is attached through a small rubber tube to a water manometer A flag floats on the water manometer, and its up and down strokes are recorded on a revolving drum It was customary to inflate the balloon system with 120 cc of air When the balloon was allowed to pass into the duodenum, a smaller quantity of air was used, usually 20 cc, occasionally 10 cc, or at times 30 cc The balloon was usually tied to the side of a Rehfuß tube in order that material could be withdrawn from or injected into the stomach at will When the balloon and one Rehfuß tube were in the duodenum, a second Rehfuß tube was usually kept in the stomach The difficulties encountered are well known to other investigators The patients soon learn to tolerate the apparatus with very little discomfort One man repeatedly swallowed four rubber tubes at one time two of them being of the Rehfuß type In the intestinal work, it was found necessary to examine the patient fluoroscopically frequently in order to detect changes in the position of the balloon This was usually done at the beginning and end of each tracing With this method, it is possible to obtain a satisfactory record of the conditions present in the fundus and body of the stomach and in the second and third portions of the duodenum, but very little evidence is obtained as regards the

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7 Poulton, E P Lancet **1** 263 (Feb 5) 1921

8 Hurst, A F The Sphincters of the Alimentary Canal, Brit M J **1** 145 (Jan 24) 1925

9 Ryle, J A Gastric Function in Health and Disease, London, Oxford Univ Press, 1926, p 961

condition of the gastric antrum, the pylorus, and the duodenal cap. These are, of course, the usual sites of lesion. It is difficult, if not almost impossible, to get a balloon to remain constantly in one of these positions during periods of filling and emptying of the stomach. Hence, it was necessary to resort to the roentgenologic method of study.

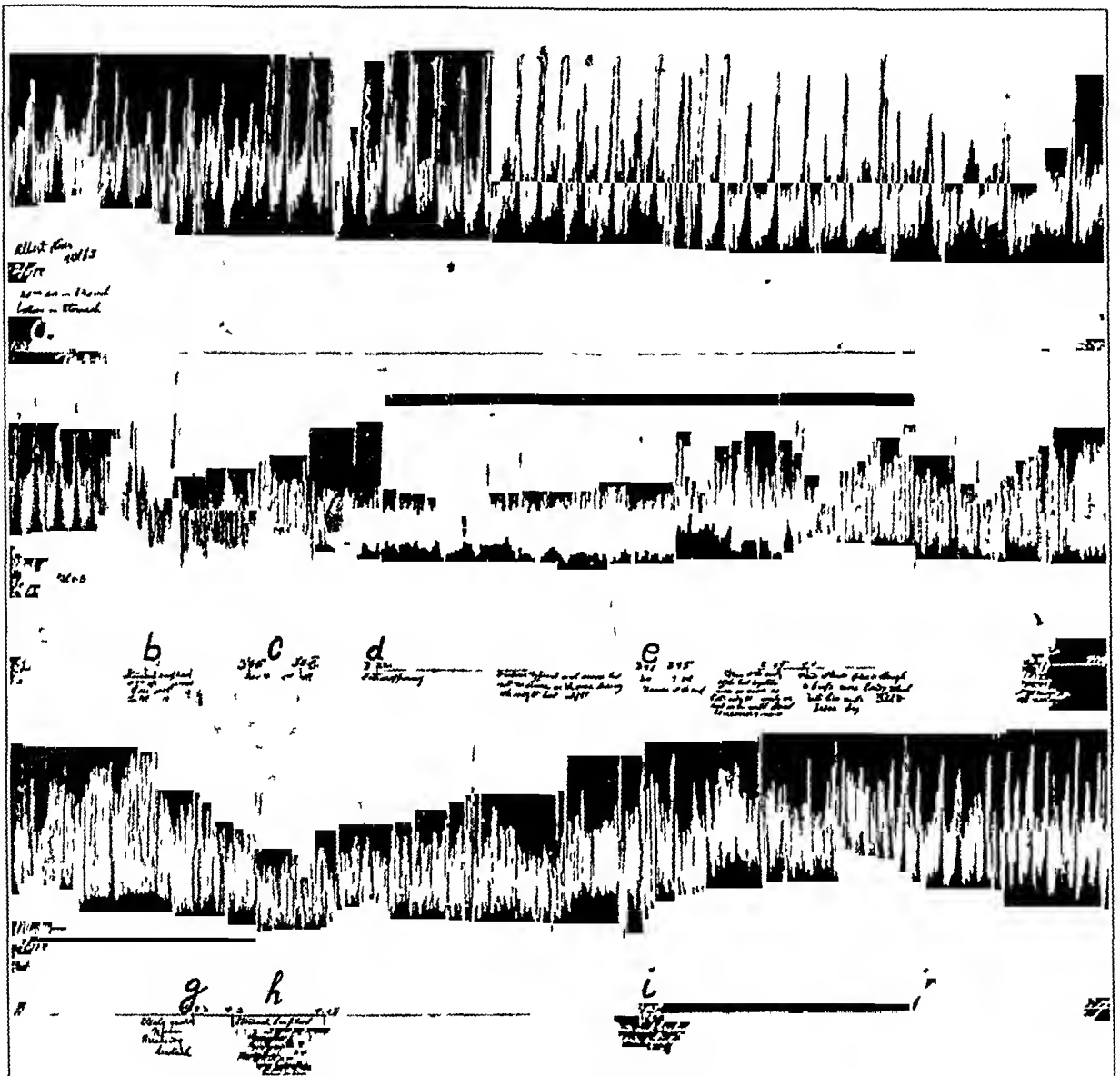


Fig 1 (experiment 157) —Consecutive record of patient with active gastric ulcer with 120 cc of air in  $6\frac{1}{4}$  inch balloon in stomach. *a*, 1 36, beginning of period of type 1 hunger contractions without pain, *b*, 2 58, stomach emptied of 10 cc of clear juice, free acidity 15, total 23, *c*, 3 05-3 08, 200 cc of 0.5 per cent hydrochloric acid solution by Rehfuess tube, *d*, 3 22, distress appearing, *e*, 3 41-3 45, distress typical and severe, 200 cc of 0.5 per cent hydrochloric acid solution, pain at once made nearly as severe as the patient can endure, *f*, 4 12, momentary stabbing pain, *g*, 4 23, steady severe pain continued, accompanied by headache, *h*, 4 25-4 28, stomach emptied of 130 cc of thick ropy liquid, free acidity 23, total 34, some relief at once, *i*, 4 45, pain and headache gone entirely, *j*, 5 05, painless contractions reappear.

Reynolds and McClure<sup>5</sup> had made fluoroscopic observations of the stomach during pain, using meat mixed with barium and waiting for spontaneous distress to appear. Sippy<sup>10</sup> had made similar studies by giving barium at a time when spontaneous distress was present and making the observations before the distress disappeared. This suggested the second method used, that of giving barium made up in a 0.5 per cent solution of hydrochloric acid to patients with pain-producing mechanisms which were known to be sensitive, and observing the changes before, during and after the induction of pain, as well as after it had been relieved by an alkali. Satisfactory results were obtained. A preliminary fluoroscopic study was made of the effect of this acid barium solution on normal stomachs.

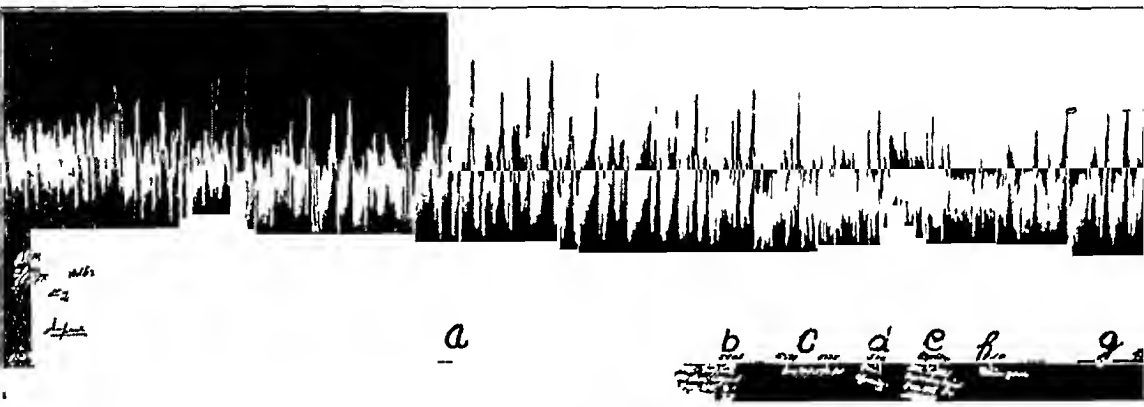


Fig 2 (experiment 169) —Record of same patient as figure 1 with 120 cc of air in  $6\frac{3}{4}$  inch balloon in stomach. *a*, 5 10, painless type 1 hunger contractions; *b*, 5 26, stomach emptied of 5 cc of clear liquid, free acidity 30, total 38; *c*, 5 31-5 35, 200 cc 0.5 per cent hydrochloric acid solution given; *d*, 5 41, pain appeared; *e*, 5 50-5 54, stomach emptied of 200 cc of clear liquid, free acidity 84, total 95; *f*, 6 10, pain entirely gone; *g*, 6 15, painless type 1 hunger contractions reappeared.

#### RESULTS OF THE BALLOON METHOD

The accompanying tracings are illustrative of the results obtained by the balloon method. The three in figure 1 represent a portion of one experiment in a patient with a sensitive gastric ulcer. The first tracing shows a period of good type 1 hunger contractions, without any distress. In the second tracing, the contractions stop (*b*) and distress appears (*d*) fourteen minutes after the injection of the acid (*c*). This distress becomes more and more severe without any pronounced increase in the intragastric tension until it becomes about as severe as the patient can stand. At times it is stabbing in character (*f*). The third tracing shows the disappearance of the pain (*i*) seventeen minutes after the emptying of the stomach (*h*) and the gradual reappearance of gastric motility without distress (*j*). The fourth tracing shows again in the same

10 Sippy, B. W. Personal communication to the author.

patient on another day the manner in which the painless type 1 hunger contractions are stopped by the injection of the acid (*c*) pain produced (*d*) without any particular alteration in intragastric tension and without marked gastric motility, the distress relieved (*f*) by emptying the stomach (*e*), and the resumption of gastric motility without distress (*g*)

In figure 2 the same phenomena are shown again. The balloon was in the stomach of a patient with a sensitive duodenal ulcer. The very vigorous hunger contractions stop before the emptying of the stomach at *c*, acid is injected at *d*, intragastric tension decreases somewhat, pain appears at *f* with no motility and with less tone than was present just previously without pain, and pain disappears at *h* after emptying the stomach at *g*.



Fig 3 (experiment 148) —Record of patient with active duodenal ulcer with 120 cc of air in 6¾ inch balloon in stomach. *a*, 4 30, beginning of period of good type 1 hunger contractions, *b*, 4 43, hunger but no other distress, *c*, 4 56, stomach emptied, nothing obtained, *d*, 4 59-5 01, 200 cc of 0.5 per cent hydrochloric acid solution given, *e*, 5 04, considerable nausea, *f*, 5 06, typical distress appeared, *g*, 5 11-5 12, distress remained the same, stomach emptied of 140 cc of clear liquid, free acidity 140, total 146, *h*, 5 20, pain gone entirely.

The tracings in figure 3 are from an experiment in which the balloon was in the descending portion of the duodenum of a patient with an active duodenal ulcer. The good duodenal contractions (*a*) are painless and are not altered by the injection of warm water into the stomach (*b*). Following the injection of acid into the stomach (*e*), spasm of the duodenum occurs but pain does not appear in this case until (*f*) after the cessation of the spasm. The pain continues without especial duodenal activity or noteworthy change in tone, and completely disappears at *h* twenty minutes after emptying the stomach at *j*. The tracings in figure 4 show the same phenomena in the descending portion of the duodenum in another patient with an active duodenal ulcer.

An entirely different type of thing is shown in the tracings of figure 5 taken with the balloon in the stomach of a patient with multiple gastric

ulcers and a highly sensitive pain-producing mechanism. In the first portion (*a*) of the first tracing, a mild continuous distress is present, not related to the gastric activity and relieved by emptying the stomach (*b*). In the remainder of this tracing, definite intermittent pains are

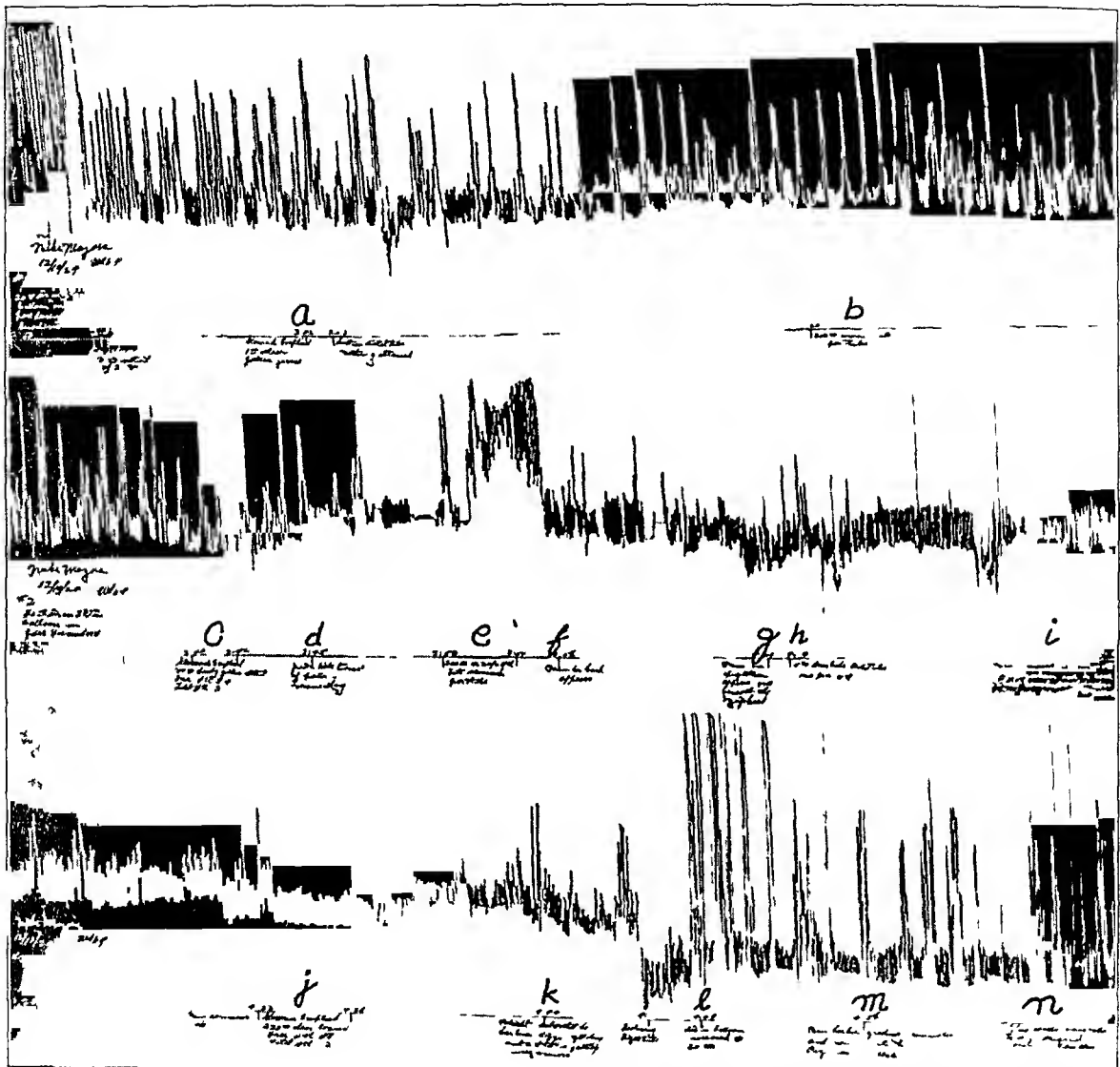


Fig 4 (experiment 96)—Consecutive record of patient with active duodenal ulcer with 10 cc of air in  $3\frac{3}{4}$  inch balloon in pars descendens duodeni: *a*, 3 02, stomach emptied of 1 cc of clear gastric juice, *b*, 3 20-3 23, continuous painless contractions unaffected by 200 cc of warm water injected into the stomach, *c*, 3 40-3 42, stomach emptied of 100 cc of cloudy gastric content, free acidity 34, total 39, *d*, 3 45, momentary twinge of pain, *e*, 3 50-3 54, 200 cc of 0.3 per cent hydrochloric acid injected into stomach, *f*, 3 56, pain in back appeared after the spasm had disappeared, *g*, 4 09, pain in epigastrium appeared, *h*, 4 10, 5 cc of clear bile in distal tube, no free hydrochloric acid, *i*, 4 20, pain remained severe both in epigastrium and back and patient concluded that "these pains are connected together," *j*, 4 33-4 36, pain remained the same, stomach emptied of 230 cc of clear liquid, free acidity 68, total 72, *k*, 4 44, patient stated that he was dizzy and that the dizziness was steadily increasing, *l*, air in balloon increased to 30 cc, *m*, 4 56, pain entirely gone, dizziness less, *n*, 5 07, fluoroscopic examination showed balloon to be in its original position in pars descendens duodeni.

registered (c) synchronous with each of the gastric hunger contractions. Six days later, good hunger contractions are present in this patient without pain, as is shown in the second tracing (a). The ulcer is still very sensitive to acid, but the pain is not so severe as at the time of the preceding experiment. In this patient apparently a more sensitive pain-producing mechanism was required for the production of pain by means of the contractions than was required for its production by means of acid.

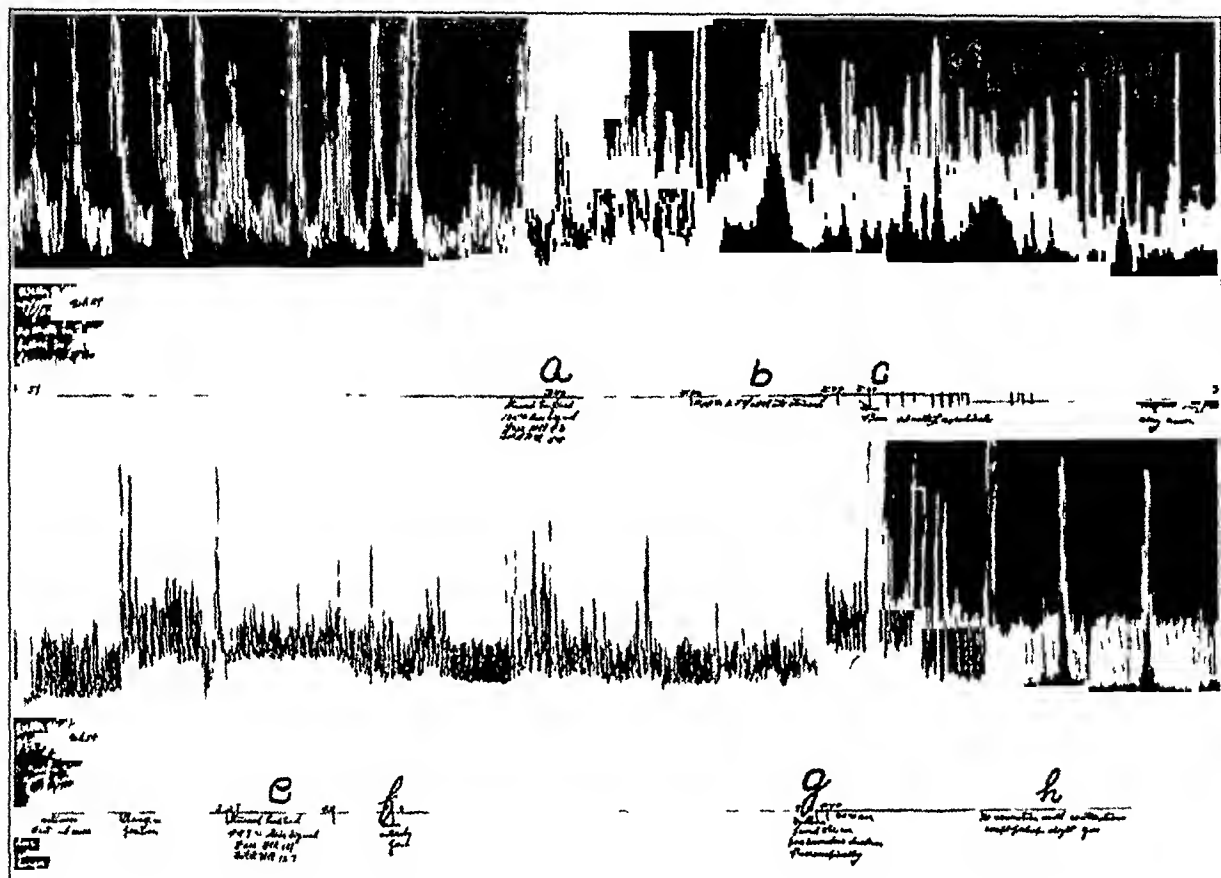


Fig 5 (experiment 249) —Consecutive record of patient with active duodenal ulcer with 20 cc of air in 3 inch balloon in pars descendens duodeni. *a*, 3 12, stomach emptied of 105 cc of clear liquid, free acidity 42, total 54, *b*, 3 20, 400 cc of 0.5 per cent hydrochloric acid solution injected into stomach, painless duodenal spasm, *c*, 3 29, remittent pain appeared, indicated by depressing the key of the signal magnet, *d*, 3 48, typical ulcer pain continued, *e*, 3 57-4 02, stomach emptied of 447 cc of clear liquid, free acidity 121, total 127, *f*, 4 05, pain entirely gone, *g*, 4 30-4 44, balloon fluoroscopically found to be in pars descendens duodeni, *h*, painless contractions.

Figure 6 illustrates a third type of case. These records are all from a patient with a chronically perforated gastrojejunal ulcer, the base of which was formed by the anterior abdominal wall, and which was further complicated by a high grade inflammatory reaction in the surrounding tissue, as was evidenced by the large, tender palpable tumor mass. This mass disappeared gradually under treatment and the exact nature of

the lesion was proved at operation by Dr Karl Meyer. In the first tracing, good type 1 hunger contractions are seen. These were productive of a "funny, grabbing sensation" (*b*) but no pain. One and a half hours later, 15 mg of histamine hydrochloride was injected subcutaneously, and an hour later pain appeared. This pain was severe and was remitting in character, as is shown in the second tracing (*c*). The paroxysms of excruciating pain are seen definitely to accompany the

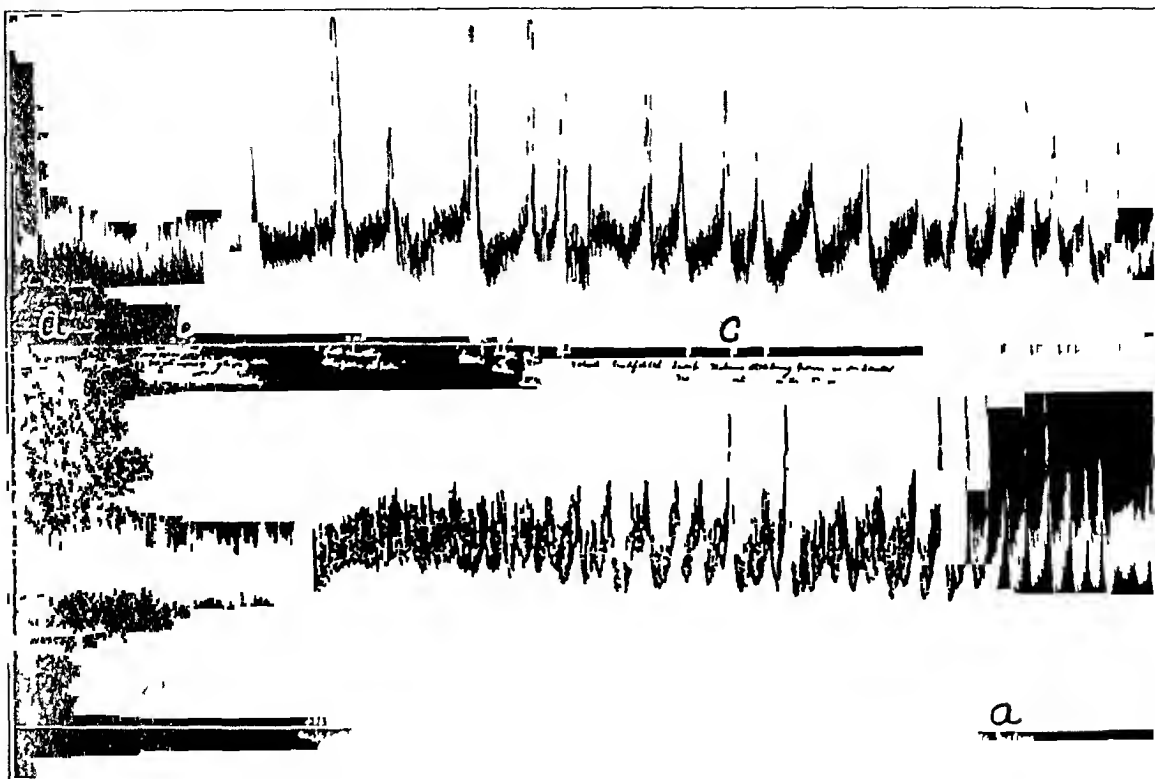


Fig 6 (experiment 225) —Upper. Record of patient with multiple superficial highly sensitive gastric ulcers with 100 cc of air in  $6\frac{3}{4}$  inch balloon in stomach (patient blindfolded), *a*, 2 52, mild spontaneous distress present, *b*, 2 59, stomach emptied of 35 cc of light brown liquid, benzidine test positive, free acidity 35, total 41, distress relieved immediately, *c*, pain with each contraction as registered, none between contractions. Lower. Record of same patient (experiment 221) six days later. *a*, painless contractions.

gastric contractions but severe pain is also present between contractions, and pain continues for twelve minutes after the cessation of the contractions (*g* to *i*). Remitting pain with a definite peristaltic factor was frequently observed in this patient. The contractions registered in this tracing are much more powerful than in the preceding one. It was repeatedly observed that when pain was produced by allowing the extremely highly acid gastric secretion to accumulate or to remain unneutralized, the contractions would become more powerful. Acid seemed to sensitize the gastric motor mechanism as well as the sensory

mechanism This is evident in the first two tracings The third was taken an hour later, and it shows the reverse condition Large doses of alkali had been given to neutralize the acid and relieve the pain The gastric secretion was so excessive that the effect of the alkali was of brief duration At 6 50 (*j*) the stomach was emptied of 95 cc of liquid with a free acid of 93 Pain appeared at once (*k*) in spite of the emptying, severe, remitting in type, and accompanied by intense muscular activity The pain was gradually relieved at *n* by heavy calcined magnesia and sodium bicarbonate (*l m*), and at the same time the muscular activity became less intense It might be reasoned that the decrease in the pain was due to the decrease in the muscular activity This may be partly true Certainly the severest paroxysms of pain were synchronous with the most intense muscular activity In the fourth tracing, however made after ten days of antacid therapy, equally intense muscular activity is evident, but without pain The gastric free acidity at this time was low 23 This suggests that intense muscular activity is an adequate stimulus to the pain-producing mechanism only when this mechanism has been sensitized by hydrochloric acid The definitely more intense muscular activity suggests that this acid sensitization may effect not only the sensory but also the motor mechanism

It was seen in the tracings of figure 4 that a very sensitive mechanism may be stimulated by motor activity alone However six days later when the patient was having less severe spontaneous distress peristaltic activity did not produce pain but acid stimulation did A higher degree of irritability was required apparently for the production of pain by means of peristaltic (mechanical) stimulation than was required for its production by means of chemical stimulation Perhaps this higher degree of irritability was the result of acid sensitization

It is possible that the pain-producing mechanism of an ulcer may be rendered so highly irritable by factors other than acid that the peristaltic stimulus alone is sufficient to effect pain Proof of this can best be obtained by the study of the pain in ulcers with a true and complete achlorhydria I have not had the privilege of observing such a case

Table 1 shows the total relationship observed between pain and peristaltic activity, the different locations of the balloon being given Pain without contractions was observed 198 times in all, whereas pain synchronous with the contractions was seen only nineteen times

Table 2 represents a summary of the types of pain encountered in the study and the relative frequency with which a contraction factor was demonstrated in each In 91.24 per cent of the pain no contraction factor was demonstrated

EFFECT OF STARVATION AND INSULIN

The great majority of hunger contractions obtained were type 1. More powerful waves were seldom seen. The periods of starvation were usually from eighteen to twenty-four hours, but the possibility existed that if the starvation period were lengthened the waves might become more powerful and be productive of pain. It is a well-known clinical fact, however, that the pain of ulcer usually disappears on

TABLE 1—*Relation of Pain to Contractions*

	Gastric	Duodenal	Total
Pain Without Contractions			
1 Constant Type			
(a) Stomach	88	62	150
(b) Pars descendens duodeni	12	18	30
(c) Pars inferior duodeni	1	3	4
2 Remittent Type			
(a) Stomach	2	4	6
(b) Pars descendens duodeni	1	1	2
3 Intermittent Type			
(a) Stomach	2	1	3
(b) Pars descendens duodeni	3	0	3
Total	109	89	198
Pain Synchronous with Contractions			
1 Constant Type			
(a) Stomach	0	0	0
(b) Pars descendens duodeni	0	0	0
2 Remittent Type			
(a) Stomach	15	0	15
(b) Pars descendens duodeni	2	0	2
3 Intermittent Type			
(a) Stomach	2	0	2
(b) Pars descendens duodeni	0	0	0
Total	19	0	19

TABLE 2—*Summary of Relation of Pain to Contractions*

Type of Pain	Frequency of Occurrence, Percentage	Contractions		
		(a) The Only Factor, Percentage	(b) A Partial Factor, Percentage	(c) No Factor Demonstrated, Percentage
Constant	84.79	0	0	100
Remittent	11.52	0	65.22	34.78
Intermittent	3.69	25	—	75
Total relationship		0.92	7.84	91.24

starvation. Nevertheless experiments were carried out to decide this point. In some the blood sugar was further depleted by insulin, Bulato and Carlson<sup>11</sup> having shown that in normal animals insulin tends to increase gastric tone and motility.

Two patients with sensitive gastric ulcers were starved for four days without experiencing pain. One was then given 25 units of insulin, and the other 30 units. Insulin reactions resulted in both cases, but there was no pain and no marked increase in the strength of the hunger

11 Bulato, E., and Carlson, A. J. Contributions to the Physiology of the Stomach, Influence of Experimental Changes in Blood Sugar Level on Gastric Hunger Contractions, *Am J Physiol* 69:107 (June) 1924.

contractions Both were highly sensitive to acid at the end of the period Three patients with duodenal ulcers were starved for three days each without the development of ulcer pain or unusually powerful hunger contractions All remained very sensitive to acid A fourth patient with duodenal ulcer was starved for three days without noteworthy increase in the intensity of his hunger contractions This patient did have ulcer pain at times during the period of starvation, but it was shown to be related to an unusually large amount of fasting gastric secretion with a high free acidity, and not to peristaltic activity

#### EFFECT OF ATROPINIZATION AND INTRAVENOUS GLUCOSE

Attempts were made to render the pain-producing mechanism unresponsive by means of atropinization, but without success Neither could it be affected by intravenous injections of glucose, although Bulato and Carlson<sup>11</sup> have shown that intravenous injections of dextrose tend to inhibit gastric tone and motility in normal animals These methods combined were also ineffective, as is illustrated in the following protocol

EXPERIMENT 422—*Pyloric ulcer with obstruction, tincture of belladonna, 10 minims four times a day for four days, 15 minims three times on day of experiment, dryness of mouth but no blurring of vision*

4 00 p m, ward supper  
 8 30, slight pain present  
 8 40, atropine sulphate, grain  $\frac{1}{75}$ , hypodermically  
 8 53, stomach emptied by Ewald tube of 530 cc of gruel, free acid 54, total 92  
 9 05, distress less, but still present Blood sugar 98 mg per hundred cubic centimeters of blood  
 9 08, stomach emptied by Rehfuess tube of 10 cc of gruel, free acid 20, total 49  
 9 10, distress gone  
 9 12, 200 cc of 0.5 per cent hydrochloric acid solution per Rehfuess tube  
 9 20, slight pain appeared  
 9 22-9 28, 250 cc of 20 per cent dextrose solution intravenously  
 9 58, blood sugar 150 mg per hundred cubic centimeters of blood  
 10 30, pain still present Stomach emptied of 250 cc of thin gruel, free acid 83, total 95  
 10 40, pain no better Stomach emptied of 20 cc of thin gruel free acid 74, total 97  
 10 50, pain gone

#### RESULTS OF THE ROENTGENOLOGIC METHOD

As has been stated, the balloon method gives evidence only of intra-gastric tension, and of the motility and tone of the body of the stomach and of the second and third portions of the duodenum It gives very little evidence as regards the duodenal cap, the pylorus, and the antrum of the stomach The other methods described above give only indirect evidence of the conditions present in these regions Roentgenologic study affords direct evidence of the state of the entire stomach, the pylorus, and the first part of the duodenum

The results here reported have been corroborated by Dr C A Matthews, roentgenologist of the Cook County Hospital, and by Dr E S Blaine, roentgenologist of the National Pathologic Laboratories and consulting roentgenologist to the Cook County Hospital. Dr Blaine took several complete sets of plates in his own laboratory as additional evidence.

Twenty-eight normal stomachs were examined with the solution of barium sulphate and 0.5 per cent hydrochloric acid. As a rule, the acid solution produced slightly more spasm of the duodenum than did the neutral solution, but the difference was relatively small. At times, the duodenal cap was as large and well filled with the acid solution as is ever the case with neutral solutions. It was interesting to note the rapid rate at which this solution might be emptied from the stomach in cases of achylia gastrica. This observation furnishes evidence regarding the control of the pylorus and also regarding the hyperperistalsis so commonly noted in these stomachs.

Forty-eight stomachs with ulcer defects were observed with the acid solution. Of these forty-eight, thirty were studied both during the presence of pain and after the pain had been relieved by an alkali. No phenomena were observed during the presence of pain which were not observed during its absence. Frequently the pylorus remained closed for several minutes, but this occurred with the buttermilk barium also and was not accompanied by pain. Gastric peristalsis was very active at times and absent at times, but entirely irrespective of the presence or absence of pain. Similarly no relationship could be determined between the condition of the cap and the presence or absence of pain, except that in duodenal ulcers pain did not appear until barium passed the pylorus. At one time, in a case of duodenal ulcer, spasm of the entire gastric antrum was noted without pain. At another time, in a sensitive gastric ulcer, spasm of the antrum was noted with excruciating pain, but the pain was also excruciating at other times when no spasm of the antrum was to be seen. The entire lack of relationship between peristalsis, pylorospasm, spasm of the cap, and pain, is well illustrated in the photographs. It must be remembered that while this method gives no evidence of the intragastric tension, the balloon method did afford that information.

In figure 7 there is very little peristalsis evident in either film, the pylorus is open, the duodenal cap is well filled, and a definite niche is seen on the lesser curvature side. The cap is somewhat smaller in the picture taken during the presence of pain than it is in the later one taken after the pain had been relieved by the administration of an alkali. Nevertheless, it is difficult to see evidence here of pylorospasm or of duodenal spasm sufficient to produce pain.

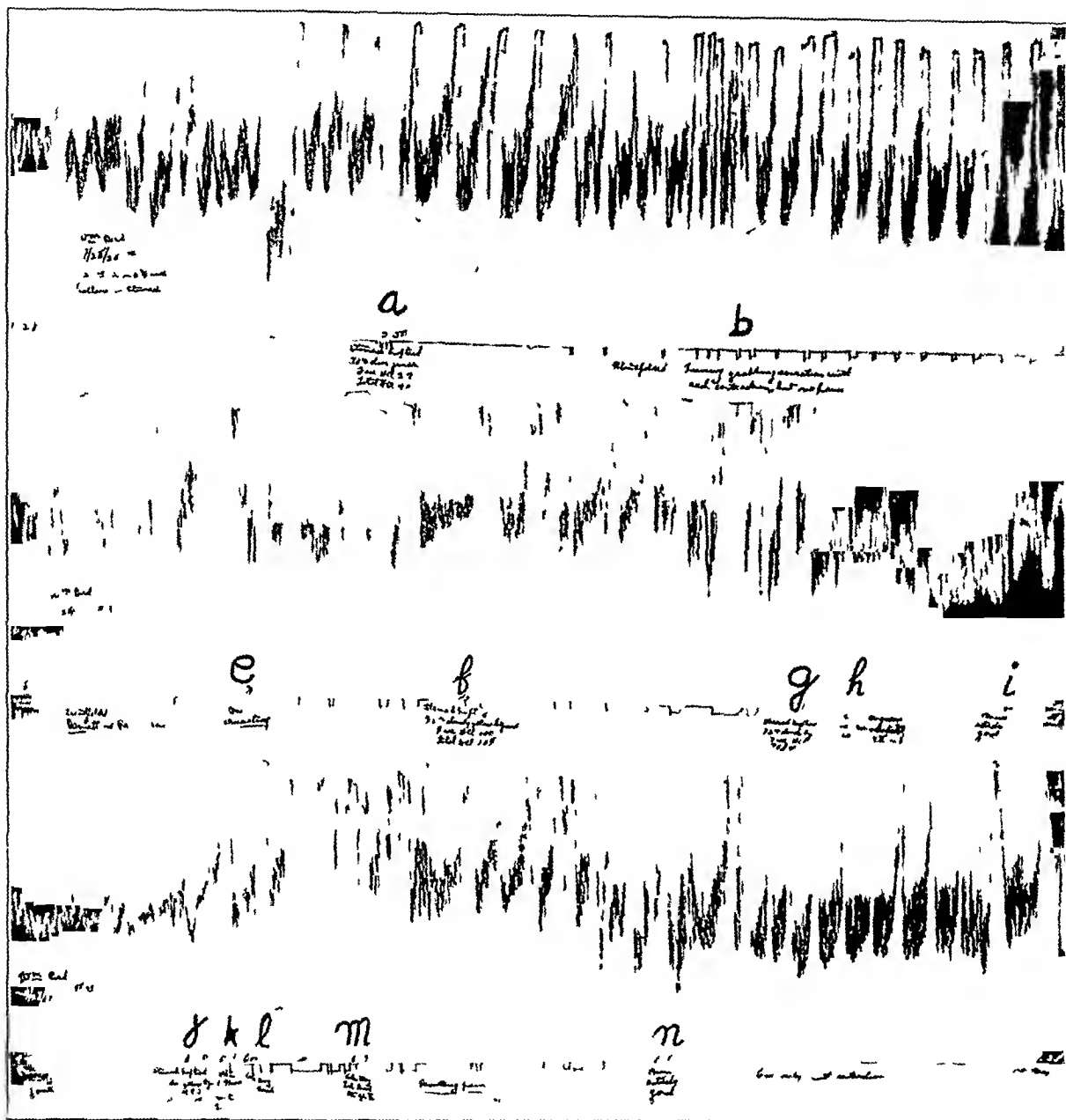


Fig 7 (experiment 375) —Record of patient with highly sensitive chronically perforated jejunal ulcer, with extensive inflammatory swelling (tracings 2 and 4 omitted from consecutive series), the patient was blindfolded, 120 cc of air in  $6\frac{3}{4}$  inch balloon in stomach a, 2 50, stomach emptied of 30 cc of clear juice, free acidity 27, total 40, b, "funny, grabbing" sensation with each contraction as indicated, but no pain, c, 3 56 (not shown), 15 mg of histamine hydrochloride injected subcutaneously, d, 4 46 (not shown), pain appeared, e, 5 06, pain excruciating—remittent, as indicated, f, 5 15, stomach emptied of 185 cc of cloudy yellow liquid, free acidity 100, total 108, g 5 32, stomach emptied of 75 cc of cloudy liquid, free acidity 93, total 101, h, 5 35, heavy calcined magnesia and sodium bicarbonate, 20 grains (13 Gm) each, given in 60 cc of water, i, 5 44, pain gone entirely, j, 6 50, stomach emptied of 95 cc of clear yellow liquid, free acidity 93, total 100, k, 6 51, pain appeared, quite severe, remitting, as indicated, l, 6 52 given calcined magnesia and sodium bicarbonate, 10 grains (0.65 Gm) each, m, 6 57, given calcined magnesia and sodium bicarbonate, 10 grains (0.65 Gm) each, n, 7 11, pain entirely gone, contractions now painless

Figure 8 illustrates the same thing in a case of duodenal ulcer with a much more extensive bulb deformity

Figure 9 shows a rather inactive stomach, a well filled duodenal cap, and an open pylorus, with a penetrating gastric ulcer. The conditions are nearly the same in the two films, one taken during pain and the other after relief had been obtained by means of an alkali. This patient had very severe pain which was entirely relieved by antacid therapy. During the course of treatment, the defect was observed to diminish in size, and finally it disappeared completely.

In the four parts of figure 10 a similar condition is seen. The cap and pylorus are widely distended during the presence of pain. Furthermore, there is no appreciable difference in the size of the lesser curvature defect in the different roentgenograms, such as one might perhaps expect to find if local spasm were a factor in determining the size of

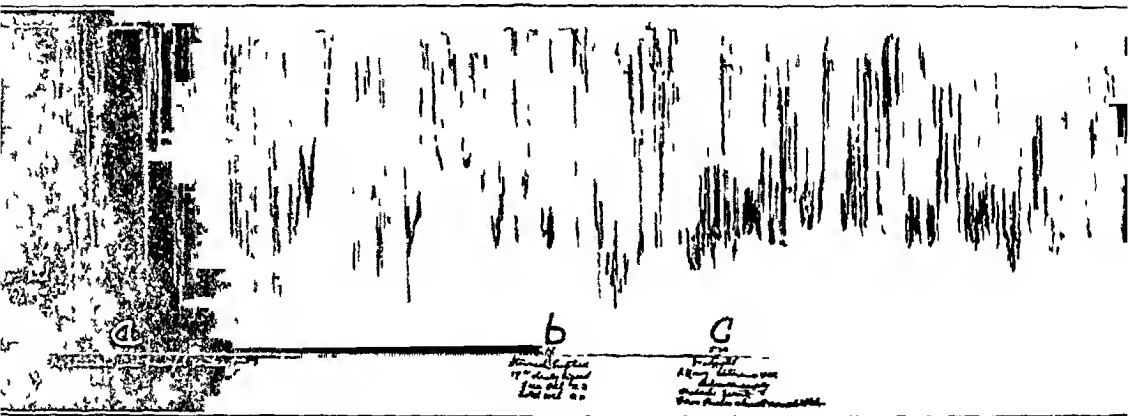


Fig 8 (experiment 395) —Record of same patient as figure 7 after ten days of intense antacid therapy with 120 cc of air in 6¾ inch balloon in stomach *a*, powerful contractions without pain, *b*, 4 40, stomach emptied of 57 cc of cloudy liquid, free acid 23, total 30, *c*, 5 00, 15 mg of histamine hydrochloride injected subcutaneously, *d* (not shown), pain did not result from the secretion induced by the histamine

the defect or in the pain. At laparotomy, a penetrating ulcer of the posterior wall of the lesser curvature was found, and a subtotal gastric resection was performed by Dr. Karl Meyer.

#### COMMENT

It has been shown that the irritant present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer, namely, hydrochloric acid, does not usually act by means of increased gastric or duodenal tone or motility or by means of pylorospasm. The pain-producing mechanism appears to lie in close relationship to the ulcer. In a relatively small group of highly sensitive mechanisms, the mechanical irritation of normal gastric peristalsis was shown to be an adequate stimulus for either the initiation or

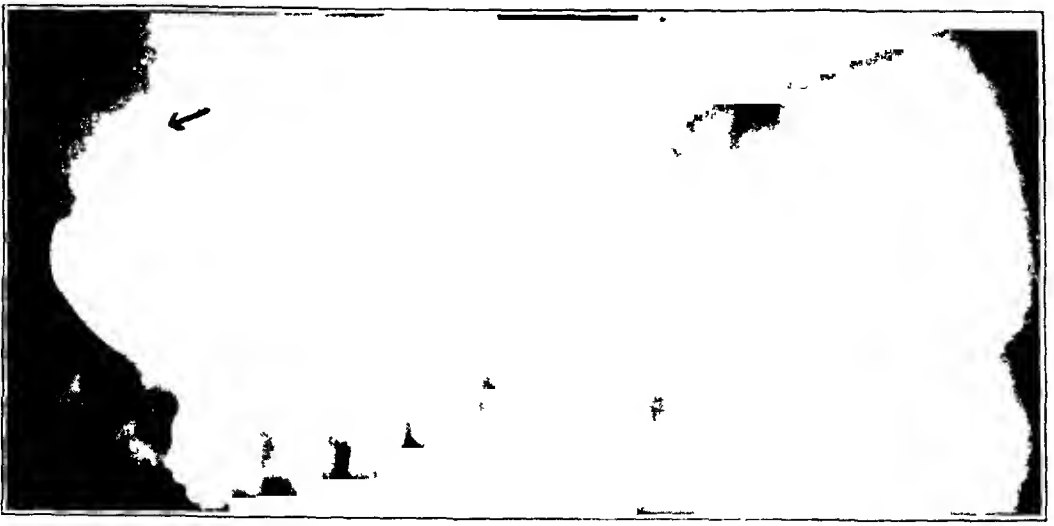


Fig 9—Active duodenal ulcer left, after barium-hydrochloric acid solution, with pain present, right, after alkali, with pain absent



Fig 10—Active duodenal ulcer left, after hydrochloric acid, with pain present, right, thirty minutes later, after alkali, with pain absent



Fig 11—Active gastric ulcer left, after barium-hydrochloric acid solution, with pain present, right, thirty minutes later, after alkali, with no pain

augmentation of the pain. This effect seemed to be dependent on previous acid sensitization. Some evidence was presented to show that the acid sensitized not only the sensory mechanism, but also the motor mechanism as well. Whether or not these mechanical stimuli may at times constitute adequate stimuli to the pain-producing mechanism in the absence of acid sensitization, has not been determined. I have not had the opportunity of studying an ulcer with true achlorhydria.

The acid may act, presumably, by producing edema in the tissues at the edge of the ulcer, by producing localized muscle spasm or by direct acid irritation of the exposed nerve endings. The problem cannot be decided by the evidence available at present.

#### CONCLUSIONS

The pain-producing mechanism is intimately associated with the ulcer.

It is not usually dependent on (a) gastric tone or motility, (b) duodenal tone or motility, (c) pylorospasm.

Under certain conditions, normal gastric peristalsis may constitute an adequate stimulus to the pain-producing mechanism.

Evidence is offered to show that hydrochloric acid may sensitize both the sensory and motor mechanisms.

The rapid emptying of 0.5 per cent hydrochloric acid solutions by stomachs with complete achylia gastrica (pernicious anemia) is noted.

#### IV THE PRODUCTION OF PAIN BY THE DISTENTION OF A BALLOON IN THE INTESTINE

During the course of the previous work, occasional attempts were made to produce distress by distention of the balloon at various levels in the intestine. The pressure used was not accurately measured, nevertheless, the results obtained are of interest. It was not difficult to produce distress in this fashion, but it was difficult to gage the intensity of the pain. It would usually come on quickly, and would rapidly become very severe. One of the greatest difficulties encountered was to produce distress of the proper severity for the patient to compare with his ulcer pain. Pains of the same type, due to the same cause, and situated in the same place, may not be recognized as of the same type if there be a great difference in their intensity.

Table 3 is a summary of the results obtained. Distress that was typical as regards type and location, although not necessarily as regards severity, was produced twenty-two times, whereas atypical distress was produced twenty-three times. Most of the tests were made at a time when the ulcer was known to be acid sensitive, but the same results were obtained later when it was found to be insensitive, and in one case, four months after the ulcer and half of the stomach had been

resected. It is particularly noteworthy that in this one case the patient still described the distress produced by distention of the balloon as his old ulcer distress, typical in type and location.

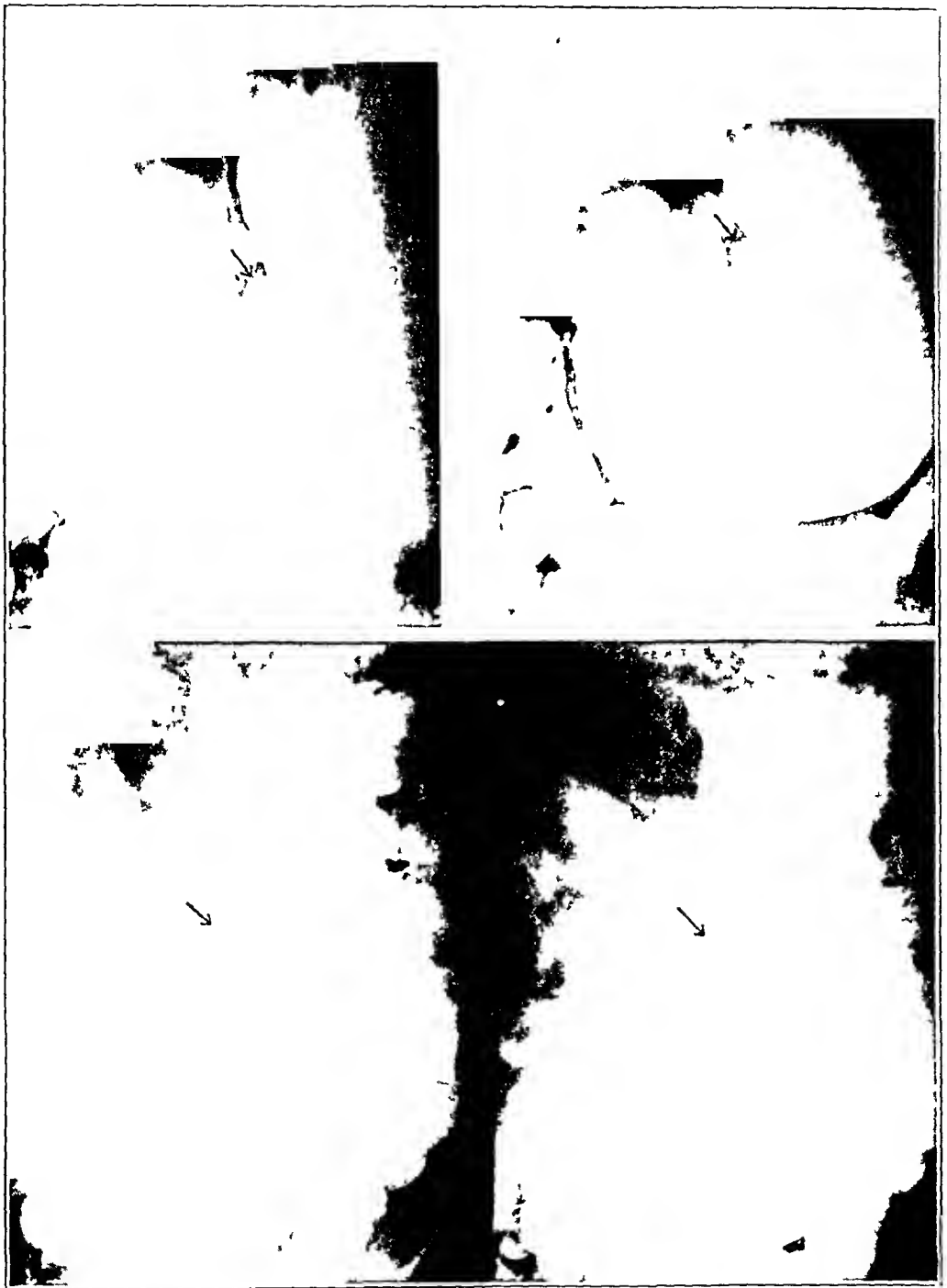


Fig 12—Active gastric ulcer upper left, pain present, upper right, pain absent, lower left, pain present, lower right, pain present

In view of the fact that it was still possible to produce typical ulcer distress by distention of a balloon in the intestine of patients with acid-insensitive duodenal ulcers and in one instance after resection of the

ulcer, the pain can hardly be interpreted as being due to reflex spasm about the ulcer. The problem of "pain memory" may be involved, nevertheless, these experiments seem to indicate a poor power of localization and differentiation of distress arising from different but adjacent portions of the intestine and produced in different ways.

## V THE PAIN OF GASTRIC CARCINOMA

Certain observations were made during the course of this work on the mechanism of pain in gastric carcinoma. Carcinoma is the only other common gastric ulcerating lesion. Clinically, it may produce pain of identically the same type and location, with the same relationship to food taking and the same relief from emesis, alkalis and eating as that

TABLE 3—*Distention of the Balloon in the Intestine*

Typical Distress Produced (Number of Times)	Gastric	Duodenal	Total
1 When Acid Sensitive			
(a) Pars descendens duodeni	2	10	12
(b) Pars inferior duodeni	2	1	3
(c) Jejunum (first portion)	—	2	2
2 When Acid Insensitive			
(a) Pars descendens duodeni	—	—	—
(b) Pars inferior duodeni	—	2	2
3 After Resection of Ulcer			
(c) Jejunum (first portion)	—	3	3
Total	4	18	22
Atypical Distress Produced (Number of Times)			
1 When Acid Sensitive			
(a) Pars descendens duodeni	10	5	15
(b) Pars inferior duodeni	4	2	6
(c) Jejunum (first portion)	—	2	2
Total	14	9	23

which characterizes the benign ulcer, or it may produce distress that is entirely different. It varies greatly. It may be made worse by food taking. It may be relieved only partially or not at all by emesis or alkalis. It may be severe and constant, regardless of the nature of the gastric content. These different types of pain in carcinoma may be due to different pain-producing mechanisms. In the following work, an attempt is made to differentiate these factors.

## DATA

Table 4 is a summary of the results obtained by means of hydrochloric acid injections as described in part II. The typical pain was initiated or markedly intensified by the injection in eight of the twelve cases. All of the successful results were obtained in patients who had spontaneous distress. In the three patients who had practically no spontaneous pain as a result of their gastric carcinoma, the injection of the acid failed to produce pain. There was one failure in a patient who did have a good deal of spontaneous pain and who had had pain within the preceding twenty-four hours. It is noteworthy also, that the three

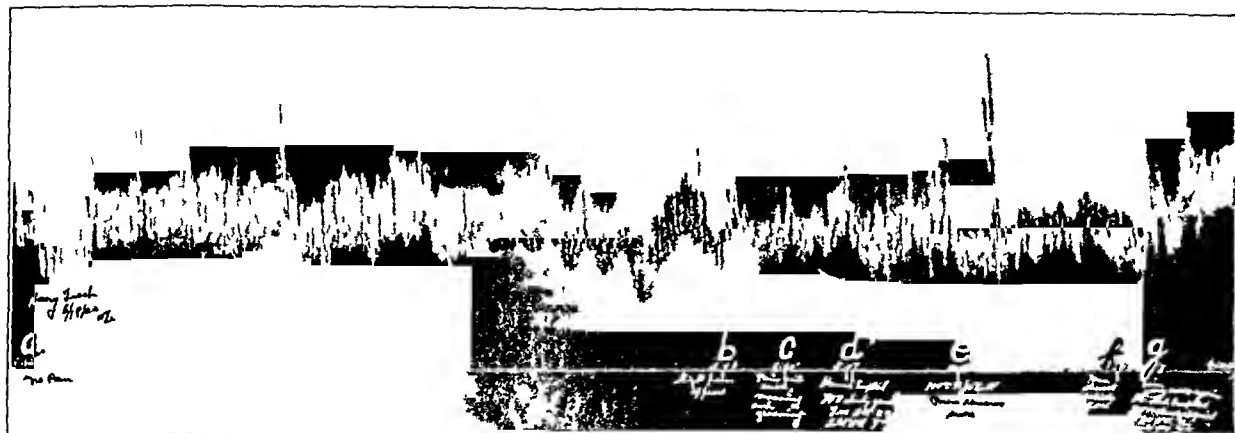


Fig 13 (experiment 306) —Record of patient with carcinoma of the antrum with 120 cc of air in 6¾ inch balloon in stomach *a* (blurred), 5 15, no pain *b*, 5 43, slight pain appeared, *c*, 5 45, pain quite severe, patient moaning and groaning, *d*, 5 47, stomach emptied of 80 cc of cloudy gruel, free acidity 24, total 87, *e*, 5 50, pain remained the same, given 100 cc of tenth normal sodium hydroxide, *f*, 6 07, pain almost entirely gone, *g*, 6 17, pain very severe again, stomach emptied of 85 cc of cloudy liquid, free acidity 21, total 37

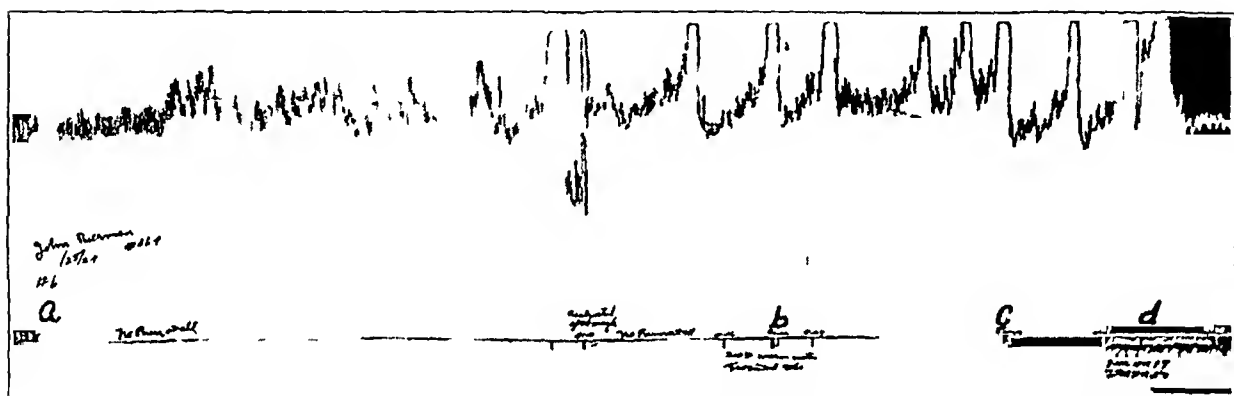


Fig 14 (experiment 68) —Sixth tracing of patient with carcinomatous ulcer of the stomach (patient blindfolded) *a*, 3 37, good tone but no motility or pain, *b* and *c*, slight twinges of pain—no pain with the other contractions, *d* (blurred), 4 21-4 26, stomach emptied of 180 cc of chocolate colored liquid, free acidity 17, total 53

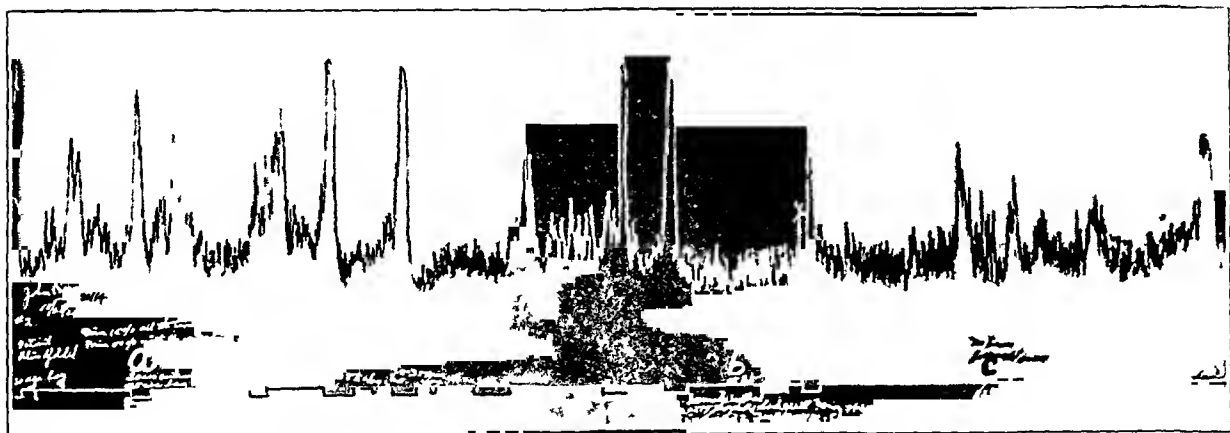


Fig 15 (experiment 68) —Second tracing *a* (blurred), 15 per cent of his usual pain continuously, 50 per cent of his usual pain synchronous with the contractions, as indicated, *b*, 12 35, stomach emptied of 315 cc of chocolate colored gruel, positive benzidine test, free acidity 22, total 102, *c*, 12 52, pain entirely gone, 5 58, pain returned, 6 05, stomach emptied of 25 cc of cloudy juice, free acidity 35, total 47, 6 10, 200 cc of twentieth normal sodium hydroxide by Reh-fuss tube, 6 17, pain entirely gone, 8 18, 10 cc of sample of gastric content removed, free acidity 3, total 19

painless carcinomas occurred in persons whose Ewald test meals contained no free hydrochloric acid. Similarly, patients 1, 3, 4 and 5 were completely or greatly relieved of their pain by antacid therapy. These were the cases with the highest Ewald acidities. Patient 8, with no free acid evident in the Ewald test, obtained almost no relief from antacid therapy, and patient 6, with a low Ewald free acidity, also obtained almost no relief.

TABLE 4—*Gastric Carcinoma*

Case	Pain    No Pain		Ewald Acidity	Spontaneous Pain	Relief from Antacid Therapy	Remarks
1	1		30-70	Severe	Partial	Carcinomatous ulcer resected
2	2		20-63	Severe		Extensive carcinoma at laparotomy
3	2		40-74	Severe	Complete	Roentgen ray diagnosis carcinoma of antrum, died 6 months later
4	1		43-63	Severe	Nearly complete	Pyloric carcinoma resected
5	4		23-48	Severe	Complete	Massive carcinoma, died 3 months later
6	6		15-28	Severe	Slight	Roentgen ray diagnosis carcinoma of cardia, died 1 month later
7	1		0-70	Severe		Carcinoma with obstruction at laparotomy
8	1		0-30	Severe	Slight	Carcinoma of posterior wall found at laparotomy
9		1	High	Severe		Roentgen ray diagnosis carcinoma of posterior wall
10		1		Slight		Painless carcinoma of stomach with ascites
11		1	0	None		Pyloric carcinoma with obstruction found at laparotomy
12		1	0-99	None		Carcinoma of pylorus found at laparotomy

The following protocol from case 2 illustrates the production of carcinoma pain by the injection of an acid.

2 55, stomach emptied of 100 cc of chocolate tinged gruel free acidity 15, total 28

3 10, 200 cc of 0.5 per cent hydrochloric acid solution given by Rehfuess tube. Pain appeared at once, burning and pressing in nature, gradually increasing.

3 20, pain was now more severe than he had ever had.

3 45, pain continued, but was less severe. Stomach emptied of 120 cc of dark brown liquid, free acidity 120, total 124.

3 54, pain disappeared.

The following protocol illustrates this also, and shows how relatively low acidities may be sufficient to initiate pain in sufficiently sensitive mechanisms.

#### EXPERIMENT 320—*Carcinoma of the antrum*

3 55, stomach emptied of 40 cc of thick gruel, no free acid (after alkali).

4 05, 200 cc of 0.25 per cent hydrochloric acid solution given by Rehfuess tube.

4 18, pain appeared.

4 25, pain severe. Ten cubic centimeter sample removed from stomach, free acidity 26, total 62.

- 4 30, 100 cc of tenth normal sodium hydroxide given by Reh fuss tube
- 4 38, pain entirely gone
- 4 57, pain returned, mild
- 5 00, stomach emptied of 5 cc of clear juice, free acidity 18, total 34
- 5 36, pain very severe Stomach emptied of 20 cc of cloudy juice, free acidity 66, total 79
- 5 39, 200 cc of twentieth normal sodium hydroxide given by Reh fuss tube
- 5 45, pain entirely gone

These protocols show clearly that in certain cases the pain of carcinoma may be initiated by relatively low degrees of gastric acidity and be completely relieved by its neutralization in identically the same manner as that of peptic ulcer

The tracing shown in figure 11 from patient 5 shows that the pain may be entirely unaccompanied by alterations in intragastric tension or motility

The opposite type of result is seen in figure 12, patient 1, in which contractions are seen, but pain is not shown, except in two instances when the patient indicated a short intermittent type of pain coincident with two contractions

Figure 13 from patient 1 shows remittent pain, in which the exacerbations of the pain are synchronous with the gastric contractions The pain is relieved by emptying the stomach The patient was blindfolded during this experiment Here there is remittent pain which is definitely related to the contractions of the stomach

It is apparent, therefore, that one type of carcinoma pain may resemble the pain of peptic ulcer in that it may be initiated by an adequate degree of free acidity and relieved by neutralization of the acid, and also that in its intermittent and remittent forms it may be initiated or aggravated by gastric peristalsis There is no evidence here of a constant and continuous type of pain due solely to muscle tension The best evidence available at present pointing in this direction are the data contained in the following case report

A woman, aged 50, entered Cook County Hospital, in the service of Dr Rice, Oct 24, 1925, complaining of pain in the epigastrium and loss of weight, each of three months' duration The pain was gnawing in character, usually coming on from one to two hours after eating It appeared later after heavy meals than after light meals Eating always relieved the pain The patient was in the habit of taking two or three crackers to bed with her at night in order to relieve the distress which awakened her The effect of vomiting and of soda was unknown

An Ewald test meal showed free acid 0, total acid 10 A second Ewald meal showed free acid 0, total acid 7 A therapeutic aspiration was made at the height of pain, 22 cc of gruel showed free acidity 0, total 30 The stomach was washed with cold water Complete relief was obtained in less than ten minutes

On November 18, Dr Karl Meyer resected a superficially ulcerating carcinoma of the lesser curvature of the stomach Grossly and microscopically the tumor was an ulcerating scirrhus carcinoma The patient made an uneventful recovery

In this case there was a gnawing epigastric distress, in all probability due to the carcinoma of the stomach, and present without free acid in the gastric content obtained at the time of distress. It seems fair to assume that before coming to the hospital this distress also occurred at a time when there was no free acid in the gastric content, and that in accordance with the patient's story, it was regularly relieved by the eating of two or three crackers. It seems difficult to explain this distress on any other basis than that of muscle tension or muscular activity.

Another type of carcinoma distress is that which is unaltered by the removal of the irritants in the gastric content, and which is unaltered by those measures which commonly relieve muscle tension temporarily, such as washing out the stomach. This type of pain is usually severe and is present constantly day and night, influenced only by opiates. Fenger<sup>12</sup> commented on this type of pain and considered that it was probably due to malignant infiltration of the nerve fibers.

The distress due to gastric dilatation and distention secondary to pyloric obstruction is scarcely ever a pain and is not included in this consideration of the pain of gastric carcinoma.

The various factors, then, which are known to enter into the production of pain in carcinoma of the stomach are acid irritation of the pain-producing mechanism, muscle tension and probably malignant infiltration of the nerve fibers.

#### DESENSITIZATION OF PAIN-PRODUCING MECHANISM

The following case report is of intense interest from the standpoint of the mechanism of pain in both benign and malignant ulcerations of the gastric mucosa.

A man, aged 47, entered Cook County Hospital, in the service of Dr. Carr, June 2, 1925, complaining of a dull aching pain in the epigastrium of two or three weeks' duration, usually occurring about 3 or 4 p. m., lasting until relieved by supper, recurring about 9 or 10 p. m., when it would be relieved by food taking again. At times the pain would be very severe. Physical examination was essentially negative except for a hard firm mass in the epigastrium, about 2 cm. in diameter, and only slightly mobile on respiration. During the weeks the patient was under observation there was a definite increase in the size of this mass.

An Ewald test meal of 75 cc. showed free acidity, 28, total acidity, 48, a motor meal of 40 cc., free acidity, 10, total acidity, 20. The Wassermann reaction was negative. Eleven of fifteen stools gave a positive benzidine test for blood. Roentgen-ray examination showed extensive carcinoma of the pars media of the stomach.

On June 14, 1925, a soft diet was ordered. On June 18, the severe daily pain continued. An acid test produced severe pain (experiment 320). On June 19, the

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12 Fenger, Christian. On Cancer of the Stomach, *The Collected Works of Christian Fenger*. Philadelphia, W. B. Saunders Company, 1912, pp. 126-138.

Sippy treatment was started. The day time relief from pain was immediate and complete. The night pain continued. On June 23, an acid test produced severe pain. On June 24, an acid test produced severe pain.

On July 8, the patient was entirely pain-free, day and night, and was gaining weight. On July 10, an acid test produced slight pain only. On July 14, an acid test of 400 cc of 0.5 per cent hydrochloric acid solution was given for one hour without distress. On July 17, an acid test of 600 cc of 0.5 per cent hydrochloric acid solution was given for one and one-half hours without distress. On July 24, the patient was discharged. An operation had been refused.

On August 28, the patient was readmitted for headache and swelling of the feet. The epigastric mass was markedly increased in size. He had remained on management, had gained 27 pounds (12.2 Kg) in weight, and had been entirely free from pain.

On September 3, he developed right hemiplegia. On September 6, he developed terminal bronchopneumonia. Necropsy was refused.

In short, this was a case of gastric carcinoma with severe pain. The pain-producing mechanism was extremely sensitive to acid. Antacid treatment completely relieved the pain and desensitized the pain-producing mechanism to the extent that 600 cc of 0.5 per cent hydrochloric acid solution produced no distress in one and one-half hours.

#### COMMENT

It is a well known fact that many cases of carcinoma of the stomach are relatively painless. Others are extremely painful. The factors responsible for the pain are acid irritation, muscle tension and probably malignant infiltration of the nerve fibers. The pain due to acid irritation may be completely relieved by antacid therapy. The exact mechanism of pain production by means of acid irritation is no better understood in malignant ulceration than it is in benign ulceration. The mechanism of desensitization by antacid therapy is also unknown, an attractive hypothesis is that the checking of the peptic activity prevents the digestion of the slough and of poorly vitalized tissue, and thereby protects the sensitive nerve endings from the action of the chemical irritant.

#### CONCLUSIONS

Under certain conditions, the pain of gastric carcinoma can be initiated by the introduction of 0.5 per cent hydrochloric acid solution into the stomach, and be relieved by its withdrawal or neutralization.

Muscle tension is at times a factor in the pain of carcinoma.

A third type of pain is apparently due to carcinomatous infiltration of the sensory nerve fibers.

Antacid therapy will completely relieve the pain due to acid irritation, and in some instances give complete relief from the pain of carcinoma.

Antacid therapy may desensitize the pain-producing mechanism so that it is no longer sensitive to 0.5 per cent hydrochloric acid solution.

## SUMMARY OF PARTS I TO V

It is shown in part I that the question of achlorhydria in ulcer is not settled as yet. It is fairly well established that the two conditions occur together in rare instances, but the evidence as to whether or not pain is present in such cases is entirely unsatisfactory.

Evidence is offered to show that hydrochloric acid is the irritant normally present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer. Other chemical irritants may act in the same way.

It is further shown that this irritant does not usually act by means of increased gastric or duodenal tone or motility, or by means of pylorospasm. Evidence is offered to show that hydrochloric acid may sensitize both the sensory and motor mechanisms. In sufficiently sensitive ulcers, normal gastric peristalsis may constitute an adequate mechanical stimulus to the pain-producing mechanism. In all of the results of this type obtained, acid sensitization seems to have been an essential prerequisite. Whether or not such mechanical irritants may ever be adequate stimuli in the absence of acid sensitization has not been determined, for I have not had the privilege of studying a case of peptic ulcer with true and complete achlorhydria. The possibility that this may occur is suggested by the type of pain seen in the case of frank carcinoma of the stomach reported in which pain was present without free acid and was relieved by the eating of two or three crackers.

It is shown that in certain types of carcinoma pain the same factors are operative as in that of benign ulcer, namely, acid irritation and gastric peristalsis. A third type of carcinoma pain is thought probably to be due to malignant infiltration of the nerve fibers.

The experiments relative to the distress produced by distention of the balloon in the intestines seem to indicate that some persons may be unable to differentiate distress arising in different portions of the intestine and produced in different ways.

The exact mechanism by means of which the acid produces the pain in both benign and malignant ulcerations is not determined. It may act, presumably, by producing edema in the tissues about the edge of the ulcer or by producing very localized muscle spasm, or by direct acid irritation of the exposed nerve endings. It is impossible to decide this question at present, but certain further observations may suggest the truth. The instantaneous production of severe pain which results at times in very sensitive ulcers from the injection of the acid does not argue for the etiologic relationship of gross tissue edema to pain. Certain other characteristics of the pain make it difficult to conceive of its being due to localized muscle spasm. It may come on gradually, being scarcely noticeable at first, and then, by almost imperceptible gradations,

increase in severity to intense pain. It disappears in a similar manner. As the sensitiveness of the pain-producing mechanism decreases, the latent period increases, the severity of the pain diminishes and the pain threshold rises. This occurs in both benign and malignant ulcers. In the benign ulcer, this decrease in the sensitiveness of the pain-producing mechanism seems to be related definitely to the healing process. Carcinomas can scarcely be said to heal, but the methods which desensitize a carcinoma are those which check peptic activity, prevent digestion of the slough and of poorly vitalized tissue, and thereby presumably protect the sensitive mechanism from the action of the chemical irritant. To me these phenomena seem to suggest that the acid may act by direct irritation of exposed nerve endings rather than by the production of localized muscle spasm.

#### CONCLUSIONS (PARTS I TO V)

Peptic ulcer with true achlorhydria occurs rarely, and the question of the occurrence and type of pain in such cases is unsettled.

Hydrochloric acid is the normal stimulus to the pain-producing mechanism of sensitive peptic ulcers.

Normal gastric peristalsis may be an adequate mechanical stimulus in very sensitive ulcers.

Hydrochloric acid may sensitize both the sensory and motor gastric mechanisms.

No evidence has been found to support the view that hyperchlorhydria may cause typical ulcer pain in the absence of a definite organic lesion of the gastric or duodenal mucosa.

Exact localization and differentiation of different types of enteric pain may be very difficult, if not, at times, impossible.

Under differing conditions, acid irritation and muscle tension may be responsible for all, a part, or none of the pain of gastric carcinoma.

# GIARDIASIS IN MAN

## ITS PREVALENCE AND RELATION TO DIARRHEA AND TO GALLBLADDER DISEASE \*

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BOSTON

Dobell<sup>1</sup> has called attention to the fact that it was Leeuwenhoek in 1861 and not Lambl who discovered this intestinal flagellate of man. Leeuwenhoek discovered the organism in his own stools.

The nomenclatorial status of this flagellate has been a subject for much discussion. For a considerable period it was known as *Lambda intestinalis* (Blanchard, 1888) in honor of Lambl who rediscovered the organism in 1859, then by *Giardia intestinalis* (Lambl) Alexeieff, 1914, which Dobell believes to be its proper name, and by *Giardia enterica* by Kofoid<sup>2</sup>. In a study of this question made by Boeck and Stiles,<sup>3</sup> the conclusion was reached that *Giardia lamblia*, Stiles, 1915, and first used by Kofoid and Christiansen<sup>4</sup> was the proper scientific name of this intestinal flagellate of man.

### MORPHOLOGY

Different species of *Giardia* have been found parasitic in man, dogs, cats, rabbits, rats, mice and frogs, and while they vary from each other chiefly in their size and shape, they all have certain morphologic features in common.

*Giardia lamblia* of man is a bilaterally symmetrical and binucleate flagellate, measuring from 9 to 21 microns in length and possessing eight flagella, some of which have a portion of their length within the cytoplasm before emerging as free fibrils. The nuclei, two in number, are situated at the anterior end and in the cytoplasm in the bottom of the ventral cup shaped depression or hold-fast organ. The axostyle forms a median midrib running from a central point in the ventral, cup shaped

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\* From the Department of Comparative Pathology, Harvard University Medical School.

1 Dobell, C. The Discovery of the Intestinal Protozoa of Man, Proc Roy Soc Med **13** 1, 1920.

2 Kofoid, C. A. A Critical Review of the Nomenclature of Human Intestinal Flagellates, Cercomonas, Chilomastix, Trichomonas, Tetratrichomonas and Giardia, Univ Calif Publ Zool **20** 145, 1920.

3 Boeck, W. C., and Stiles, C. W. Studies on Various Intestinal Parasites (Especially Amebae) of Man, U. S. Public Health Service Hyg Lab Bull **133**, Washington, D. C., 1923.

4 Kofoid, C. A., and Christiansen, E. B. On *Giardia Microti* Sp. Nov., from the Meadow Mouse, Univ Calif Publ Zool **16** 23, 1925, On Binary and Multiple Fission in *Giardia muris* (Grassi), Univ Calif Publ Zool **16** 30, 1915.

depression posteriorly to the end of the body. The parabasal bodies lie posterior to the ventral depression, dorsal to and across the axostyle. Peristomal fibers border the posterior limit of the hold-fast organ.

The flagellates undergo encystment at some period in their life history. The cysts are ovoid bodies measuring from 10 to 15 microns in length and from 6 to 9 microns in width. Within the cyst are to be seen two or four nuclei, curved parabasal bodies, axostyles and the remains of the intracytoplasmic portions of the posterolateral flagella. These cysts are passed out in the feces and the finding of them is the common method for determining the presence of an infection.

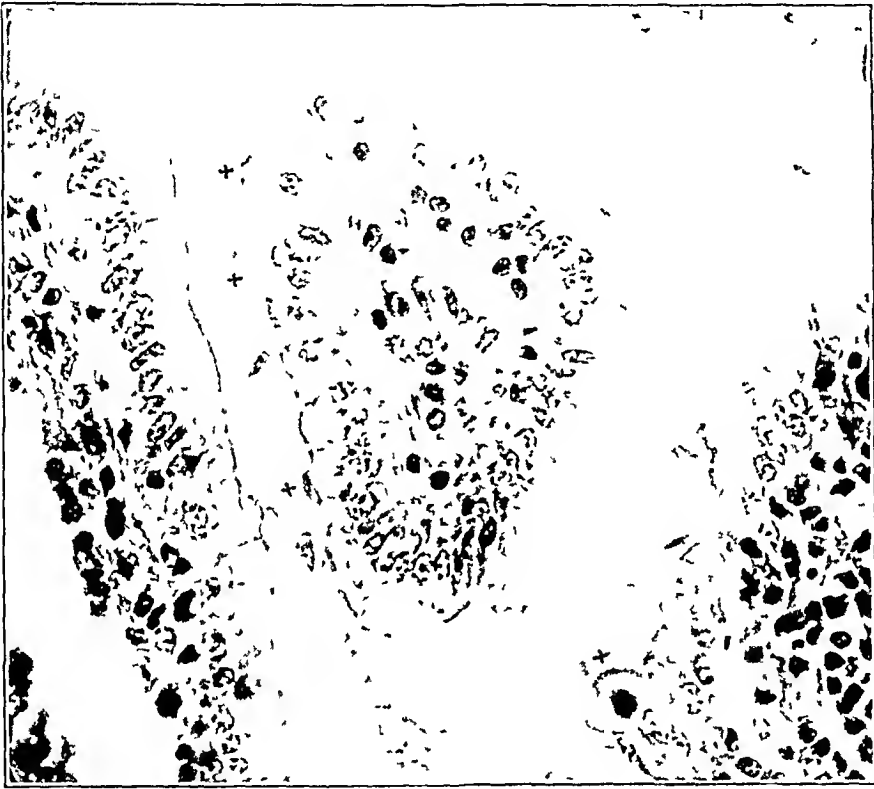


Fig. 1—Stained section of intestine from the mouse showing *Giardia muris* either attached (v) to the epithelium or free in the lumen of the crypts, intact epithelial cells with end plates even when flagellates are attached to them, and also the complete absence of all signs of irritation and inflammation, should be noted.

All species of *Giardia* live in the small intestine (duodenum and jejunum) of their host. Sections of duodenum fixed and stained reveal these organisms either attached to the epithelium (accompanying figure) by means of the ventral cup shaped depression or hold-fast organ, or in the lumen of the duodenum and that of the crypts of Lieberkuhn. They are obtained in large numbers from man by means of duodenal drainage and they remain alive for a few hours at incubator (37 C) temperature. *Giardia* has no known forcible means of invading the tissue and it is never found deep in the mucosa of the properly fixed tis-

sues, but the attachment of this flagellate to the epithelial cells has often brought up the question of their pathogenicity

PREVALENCE

From time to time various investigators and physicians reported finding this protozoan in the human feces. It was found quite frequently in children and was even said to be one of the causes of summer diarrhea, or *Lambia* enteritis, which was more often observed in the summer season. But little was known of its widespread distribution and the frequency with which it occurred in adults and children until the completion of the numerous protozoan surveys during and after the

TABLE 1—Incidence and Infection in Children and Adults

Investigators	Total Number of Cases Examined		Average Number of Examinations per Case		Total Cases Found Positive for <i>Giardia</i> , per Cent	
	Adults	Children	Adults	Children	Adults	Children
Matthews and Smith (Liverpool cases) <sup>5</sup>	1,008	548	1	1	7.0	14.1
Campbell (Bristol cases) <sup>7</sup>	178	40	2.5	1+	3.9	16.3
M. M. McNutt (Leeds cases) <sup>7</sup>	333	128	1+	1+	3.8	39.8
Macey <sup>8</sup>		89		2.0		18.0
Boeck (vide infra)		50		2.2		22.0
Boeck and Stiles <sup>3</sup>						
a State prison cases	196		1.0		2.5	
b U. S. Naval Training Station cases	711		1.0		9.0	
c U. S. troops	6,120		1.2		5.7	
Kofoed and Swezy <sup>50</sup> U. S. troops	2,876		1+		5.9	
Boeck and Stiles <sup>3</sup>						
Training School A		329		5.2		14.5
Training School B		83		5.5		50.6
Matthews and Smith <sup>6</sup>						
Dysenteric convalescents	4,068		3.0		9.9	
Same cases	4,068		5.6		16.4	
Smith and Matthews, <sup>58</sup> nondysenteric convalescents	450		2.0		6.0	

World War by European and American protozoologists. Table 1 gives a summary of some of the observations.

This table reveals the following important facts: (1) that the more examinations one makes per case, the greater will be the incidence of infection—a fact established by Dobell<sup>5</sup> and others, and well illustrated in table 1 by the results of Matthews and Smith<sup>6</sup> on their 4,068 cases of convalescent soldiers; (2) that on the basis of the same number of examinations per case *Giardia* is more prevalent in children than in adults.

5 Dobell, C. Reports upon Investigations in the United Kingdom of Dysentery Cases Received from the Eastern Mediterranean, 1, Amebic Dysentery and the Protozoological Investigation of Cases and Carriers, M. Research Commission Special Report, series 4, London, 1917.

6 Matthews, J. R., and Smith, A. M. The Intestinal Protozoal Infections Among Convalescent Dysenterics Examined at the Liverpool School of Tropical Medicine, Ann Trop Med & Parasitol 13: 83 (May) 1919.

Dobell<sup>7</sup> is inclined to believe that the statistics do not warrant this second conclusion, i. e., that more children are infected than adults, and he tries to explain the figures on the basis that the evidence of infection namely, finding the cysts in the stool, occurs more frequently in a given number of stools from children than in the same number from adults and, therefore, that the infection is easier and sooner discovered. But in a previous article<sup>8</sup> I have shown that this does not appear to be the case but that, on the other hand, an infection of *Giardia* is discovered as frequently in adults as in children in a given number of stools. We may conclude, therefore, that more children are infected than adults.

Table 1 shows that the discoverable rate of infection with *Giardia* among adults, on the basis of one examination per case, varies from around 3 to 9 per cent, while among children the rate varies from 14 to 40 per cent. Dobell,<sup>5</sup> however, and subsequently others have shown that one examination per case will discover only from one-third to one-half the actual number of infections that would be found by at least six or more examinations per case, and therefore the actual number of infected cases in any survey based on one examination per case may be estimated at from two to three times the number of discovered cases.

The incidence of infection again varies with the environment and its sanitation. This was well illustrated by Boeck and Stiles<sup>3</sup> for all the intestinal protozoa. Among the children and adults, for example, who live in intimate contact with each other in institutions the hygienic conditions of which are far below standard, a much larger rate of infection occurs than among children in an infirmary or hospital in which there is little personal contact and most desirable hygienic standards are maintained. This is also well shown (table 1) by comparing the rate of infection for the children examined by Miss Nutt (Dobell<sup>7</sup>), of whom the largest number resided in a workhouse and of whom 39.8 per cent were infected, with that of the children in the Johns Hopkins Hospital (Harriet Lane Home) examined by Maxcy<sup>8</sup> and in the Children's Hospital, Boston (table 2), examined by me in July, 1925, of whom 18 per cent and 22 per cent, respectively, were infected with *Giardia*.

It was surprising to learn at what early age children are found infected with *Giardia*. The most astounding and significant results were those of Miss Nutt (Dobell<sup>7</sup>), who examined the feces of twenty-five children of 1 year or less of age and found six of them infected. One child was as young as 3 weeks of age while the others were 3, 9, 11 and 12 months (two), respectively.

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<sup>7</sup> Dobell, C. A Report on the Occurrence of Intestinal Protozoa in the Inhabitants of Britain, Med. Research Commission Special Report, series 59, London, 1921.

<sup>8</sup> Maxcy, K. F. *Giardia* (Lamblia) Intestinalis, a Common Protozoan Parasite of Children, Bull. Johns Hopkins Hosp. **32**: 166 (May) 1921.

Matthews and Smith<sup>9</sup> found six cases of *Giardia* in seventy-nine children between 1 and 2 years of age. Maxcy found *Giardia* in a girl 22 months of age, and in 17 per cent of the children from 1 to 5 years old, and 40 per cent of those between 6 and 12 years old.

Miss Nutt found the greatest number of infections in children from 1 to 4 years of age, and in the fifty patients examined by me at the Children's Hospital, Boston (table 2), each receiving an average of 2.2 examinations, a similar result was obtained. Of the children from 1 to 5 years old examined at the Children's Hospital, 38.9 per cent were infected, as compared to 16.3 per cent of the children from 6 to 12 years of age. These results are in harmony with those of Matthews and Smith<sup>9</sup> also, but just the opposite to those reported by Maxcy, given in the paragraph above. Maxcy's patients from 1 to 5 years

TABLE 2—Incidence, Age and Sex Distribution of *Giardia Lamblia* Among Fifty Children Examined at the Children's Hospital, Boston (July, 1925) \*

Age	Total, 50		Males, 24		Females, 26	
	Positive	Negative	Positive	Negative	Positive	Negative
2 to 3	2	9	0	4	2	5
3 to 4	2	4	2	4	0	0
4 to 5	2	4	1	2	1	2
5 to 6	2	4	1	2	1	2
6 to 7	1	6	0	2	1	4
7 to 8	0	4	0	2	0	2
8 to 9	2	1	1	0	1	1
9 to 10	0	3	0	1	0	2
10 to 11	0	3	0	2	0	1
11 to 12	0	0	0	0	0	0
12 to 13	0	1	0	0	0	1
Totals	11	39	5	19	6	20

\* No other intestinal protozoa were found.

old numbered fifty-five, and those from 6 to 12 years, nineteen, while the 50 patients examined at the Children's Hospital by me were almost equally divided, numbering twenty-nine from 1 to 5 years old and twenty-one from 6 to 12 years old. It seems probable that had Maxcy examined more children from 6 to 12 years old, the incidence would have dropped somewhat and not have been as much as 40 per cent finally. An interesting point still remains in that of the children from 1 to 5 years old examined at the Children's Hospital, more—twice as many—were infected than among a similar group examined by Maxcy in the Johns Hopkins Hospital (Harriet Lane Home). The patients received the same average number of examinations (two), the technic of examination was the same, and the cases were more or less of the same heterogeneous character, the patients coming to the hospital on

<sup>9</sup> Matthews, J. R., and Smith, A. M. The Spread and Incidence of Intestinal Protozoal Infections in the Population of Great Britain. I. Civilians in Liverpool Royal Infirmary, II. Army Recruits, III. Children, *Ann Trop Med & Parasitol* **12** 349 (Feb.) 1919.

account of acute infectious diseases, nephritis, diabetes, and other diseases. There seems no satisfactory explanation for the discrepancy in the results of these two surveys.

There were no other intestinal protozoa found in the fifty children examined at the Children's Hospital. This result is singular in itself since other investigators have recorded infections of almost all the other intestinal protozoa. It is quite probable that had more examinations per case been possible, other protozoa would have been found, although even with two examinations per case, one would have expected to have uncovered other infections besides *Giardia*.

#### DISSEMINATION

The manner by which children acquire infections of *Giardia* is a matter of much speculation. It was thought for a time that rats and mice might serve as reservoirs for *Giardia lamblia*, for the majority of these rodents are to be found infected with a species of *Giardia*. Fantham and Porter<sup>10</sup> tried to prove this point and they apparently succeeded in infecting rats with *Giardia lamblia*, but most of them died. It would appear, therefore, that these animals are not efficient and proper hosts for this intestinal flagellate. Simon,<sup>11</sup> on the other hand, was unable to infect rats with the human *Giardia*, and his studies demonstrated specific differences between *Giardia* of man and rats. He concluded that human giardiasis is of human origin only.

There still remains, however, another side of this problem to be studied before the question of the etiology of human giardiasis can be definitely settled, for while it appears unlikely that the rodents serve as reservoirs for the human *Giardia*, yet it must be proved that man does not get his infection from rodents and that in him the flagellates undergo the slight change in morphology that has resulted in their being classified as a distinct species. Bearing on this point is the failure of Moritz and Holz<sup>12</sup> to infect man by feeding cysts of *Giardia* from mice. While this side of the problem will need further experimentation, it is certain, however, that human giardiasis is spread from one person to another by the ingestion of the cysts of the flagellates that occur in the feces. Man may ingest the cysts directly by contamination with feces on his fingers, food or water, or indirectly perhaps through the agency of

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10 Fantham, H. B., and Porter, A. The Pathogenicity of *Giardia* (*Lamblia*) Intestinalis to Man and to Experimental Animals, *Brit. M. J.* **2** 139 (July 29) 1916.

11 Simon, C. E. A Critique of the Supposed Rodent Origin of Human Giardiasis, *Am. J. Hygiene* **2** 406 (July) 1922.

12 Moritz, F., and Holz, H. Ueber Häufigkeit und Bedeutung des Vorkommens von *Megastoma entericum* im Darmkanal des Menschen, *München med. Wchnschr.* **39** 831, 1892.

the house fly which may feed on excreta containing the cysts and then deposit them apparently uninjured in its dejecta on food or in drinking water. The cysts live for some time in water or in moist feces, but die shortly on drying. It is very improbable, therefore, that cysts are ever air-borne in a viable state and that dissemination occurs by this route as Musgrave<sup>13</sup> stated. It was demonstrated by Wenyon and O'Connor<sup>14</sup> and Root<sup>15</sup> that the cysts might be ingested by flies and deposited in the feces apparently unharmed.

It is likely that unhygienic conditions in the family, and uncleanness on the part of parents and others in the family who handle the infant or child, are instrumental in spreading the infection to the baby, for it has been shown by the English investigators that often several members of a family are infected. The crawling, creeping children that are allowed to dirty themselves and remain so, thus encouraging flies to alight on them and their food and drink, or are themselves or their food and drink befouled by contaminated hands are undoubtedly the ones most apt to acquire this infection. Therefore, the observance of proper hygienic measures in the home and in institutions will go far in the prevention of giardiasis.

It seems that some children will later throw off their infection spontaneously, otherwise, the lower rate of infection in adults must be explained in some other manner, for as yet no efficient method of treatment has been discovered.

#### PATHOGENICITY

Protozoologists and physicians are divided in their opinion in regard to the question of the pathogenicity of *Giardia lamblia* in man. Many take the view that the organism is a harmless commensal and some hold to the other extreme view that it is always pathogenic, while still others maintain the attitude that these flagellates are pathogenic to the extent that they may extend and prolong an already existing pathologic condition because of their activities. It is my purpose in what is to follow to present a critical review and discussion of the evidence that has of late been accumulating and to evaluate this evidence as impersonally and scientifically as best I can. The question of pathogenicity has been raised more especially in cases of gastro-intestinal and chronic gallbladder disturbances.

The clinical manifestations that have been attributed to the presence of *Giardia* in man are (1) diarrhea, persistent or intermittent with inter-

13 Musgrave, W. E. Flagellate Infestation and Infections, J. A. M. A. 79:2219 (Dec. 30) 1922.

14 Wenyon, C. M., and O'Connor, F. W. Human Intestinal Protozoa in the Near East, London, 1917.

15 Root, F. M. Experiments on the Carriage of Intestinal Protozoa of Man by Flies, Am. J. Hygiene 1:131 (March) 1921.

vals of constipation, (2) chronic gallbladder disease with symptoms of epigastric or right upper quadrant pain, discomfort or tenderness, dyspepsia, belching of gas, nausea, vomiting and diarrhea, and (3) certain other obscure conditions in which the etiology is not apparent. I will now proceed to examine the evidence that tends to show that these conditions and symptoms occur in persons with infections of *Giardia lamblia*. One must be brief, however, in order to avoid unnecessary length to this article, therefore, only those data will be reviewed that I believe are important to the discussion of this question.

#### DIARRHEA

*Giardia* of man has always, except up to the recent era of protozoan surveys, been found most often in diarrheic stools. This was due to the fact that the motile organism was often abundant in such stools and because physicians as a class had not as yet recognized the encysted forms of this flagellate. The inference made was a natural one, *Giardia* must be the cause of the diarrhea, since it was not observed in formed stools, and since "no other cause was found." Various forms of treatment were administered with the result that the diarrhea cleared up, and the flagellates disappeared from the stools, a "cure" was said to have been obtained.

Later on, when the cysts were recognized it was often noted that the infection was still present even after the diarrhea cleared up, for the cysts were found in the formed stools. It was also demonstrated that in infected persons when the cysts occurred alone or even when absent in the feces the motile forms could be brought down by means of cathartics, or be obtained by duodenal drainage. It is to be seen, therefore, that the "cures" obtained were only apparent and not real.

During the World War, English protozoologists with physicians had occasion to observe the effect of many kinds of substances in hundreds of cases of infection with *Giardia*, many of which occurred along with *Endamoeba histolytica* or other intestinal protozoa in the same person.

Among the drugs tried were bismuth salicylate, phenyl salicylate, beta-naphthol, guaiacol, thymol, turpentine, emetine, calomel, methylene blue, asphenamine and other arsenicals. Wenyon and O'Connor<sup>14</sup> came to the conclusion "that no satisfactory treatment for lamblia infections exist." This opinion is shared by Dobell and O'Connor<sup>15</sup> and others. In most cases of reported "cure" with eradication of the infection, the individual has not been followed long enough to determine whether the infection is still present or not, but in a few sporadic cases in which this has been done, "cures" appear to have been obtained. In

14 Dobell, C, and O'Connor, F. W. The Intestinal Protozoa of Man, New York, 1921.

this country Kantor,<sup>17</sup> Simon,<sup>18</sup> Hollander,<sup>19</sup> Carr and Chandler<sup>20</sup> and others reported cases cured by asphenamine or neoarsphenamine, but Hollander also reported failures in other cases, and this has been the experience of Reed and Wyckoff,<sup>21</sup> and others. The substance has given indifferent results and not universal satisfaction in all cases in which it has been tried (Goiffon and Roux<sup>22</sup> and Cade and Hollande<sup>23</sup>).

The intra-intestinal thermal therapy of de Rivas<sup>24</sup> still awaits confirmation and endorsement by other physicians as an effective method of treating *Giardia* infections.

The question may well be asked, then, does *Giardia* actually cause diarrhea, and if so, how?

In trying to find an answer I may resort either to my own opinions based on isolated cases for evidence for proof or to statistical studies of protozoan surveys covering hundreds of cases. I shall do both to some extent.

#### STATISTICAL EVIDENCE

The surveys of Matthews and Smith,<sup>9</sup> Maxcy<sup>8</sup> and my present one covering fifty children from the Children's Hospital reveal the fact that generally children under 1 year of age do not become infected with *Giardia*. The only exceptions to these observations are those of Miss Nutt (Dobell<sup>7</sup>), who found six cases of infection among twenty-five infants less than 12 months of age.

From table 3 it may be seen that *Giardia* infections are usually acquired after the first year of life, and increase to a maximum at about the age of 6 or 7, although the incidence is still high in children up to 12 to 16 years of age compared to the adult rate of infection (table 1). Matthews and Smith<sup>9</sup> showed that the rate of infection among 275 children from 1 to 5 years of age was 16.4 per cent as compared to 14.3 per cent among 223 children 5 to 12 years old.

Now, then, if *Giardia* caused diarrhea in children, it would appear from the data in table 3 that diarrhea would be more prevalent among

17 Kantor, J. L. *Lamblia (Giardia) Infection Associated with Cholecystitis*, Arch Int Med **32** 693 (Nov.) 1923.

18 Simon, S. K. *Further Observations of Lamblia Intestinalis Infestation and Its Treatment*, South M. J. **15** 458 (June) 1922.

19 Hollander, Edward. *Giardia Intestinalis Infection*, Arch Int Med **32** 522 (Oct.) 1923.

20 Carr, E. I., and Chandler, W. L. *Successful Treatment of Giardiasis in Man with Neoarsphenamine*, J. A. M. A. **74** 1444 (May 22) 1920.

21 Reed, A. C., and Wyckoff, H. A. *Intestinal Protozoa in Clinical Practice*, M. Clin. N. Amer. **5** 391 (Sept.) 1922.

22 Goiffon, R., and Roux, J. C. *Les enterites a Lamblia*, Arch. d. mal. de l'app. digestif **9** 601 (April) 1918.

23 Cade, A., and Hollande, A. C. *L'Enterite a "Giardia (Lamblia) intestinalis"*, Arch. d. mal. de l'app. digestif **10** 193 (July) 1919.

24 De Rivas, D. *The Effect of Temperature on Protozoan and Metazoan Parasites and the Application of Intra-Intestinal Thermal Therapy in Parasitic and Other Affections of the Intestine*, Am. J. Trop. Med. **6** 47 (Jan.) 1926.

children in the age group of 1 to 6 or 7 than among older children and adults. But the fact is that the incidence of *Giardia* infections *actually increases* from year to year in this group of children while the *incidence of diarrhea decreases*.

Another factor must therefore be sought as the cause of diarrhea of infancy and childhood, and this has been definitely known for a long time to be dysentery bacilli as shown by the work of Duvall and Bassett,<sup>25</sup> Flexner and Hall,<sup>26</sup> Davison<sup>27</sup> and Wollstein<sup>28</sup>

It must be concluded therefore that statistically, at least, *Giardia* does not appear to be the cause of children's diarrheas. This is borne out by the observations of Matthews and Smith,<sup>9</sup> who state that "the intestinal

TABLE 3—*Age Distribution of Giardiasis in Children*

Age	Matthews and Smith <sup>9</sup>		Maxcy <sup>8</sup>		Boeck		Total		Percent of Total Cases Examined
	Number Cases Examined	Number Cases Infected	Number Cases Examined	Number Cases Infected	Number Cases Examined	Number Cases Infected	Number Cases Examined	Number Cases Infected	
0 to 1	50	0	15	0	0	0	65	0	0
1 to 2	79	6	15	1	0	0	94	7	7.4
2 to 3	74	18	12	1	11	2	97	21	21.6
3 to 4	56	9	12	1	6	2	74	12	16.2
4 to 5	66	12	10	4	6	2	82	18	21.9
5 to 6	43	5	6	1	6	2	55	8	14.5
6 to 7	41	10	4	1	7	1	55	12	21.8
7 to 8	36	4	4	3	4	0	44	7	15.9
8 to 9	42	5	2	1	3	2	47	8	17.0
9 to 10	27	4	2	0	3	0	32	4	12.5
10 to 11	23	3	1	0	3	0	27	3	11.1
11 to 12	8	1	4	1	0	0	12	2	16.6
12 to 13	0	0	2	0	1	0	3	0	0
Total	518	77	89	14	50	11	687	102	14.8

protozoa are in no way connected with the occurrence of summer diarrhea in children," and by the findings of Maxcy<sup>8</sup>

My own observations on the fifty children examined at the Children's Hospital were quite similar in character. Diarrhea was a chief complaint in only two cases, one of which had a *Giardia* infection and the other had not. In both these cases the diarrhea was due to an improper diet and vanished when it was changed.

25 Duvall, C. W., and Bassett, V. H. The Etiology of the Summer Diarrhea of Infants. A Preliminary Report, *Am. Med.*, Philadelphia, **4**: 417, 1902. *Studies Rockefeller Inst. M. Research* **1**, 1904.

26 Flexner, S., and Holt, L. E. Bacteriological and Clinical Studies of the Diarrheal Diseases of Infancy with Reference to the *Bacillus Dysenteriae* (Shiga), *Studies Rockefeller Inst. M. Research* **1**, 1904.

27 Davison, W. C. Bacillary Dysentery in Children, *Bull. Johns Hopkins Hosp.* **31**: 225 (July) 1920, A Bacteriological and Clinical Consideration of Bacillary Dysentery in Adults and Children, *Medicine* **1**: 389, 1922.

28 Wollstein, M. A Bacteriologic Study of Acute Diarrhea in Young Children, *Am. J. Dis. Child.* **25**: 310 (April) 1923.

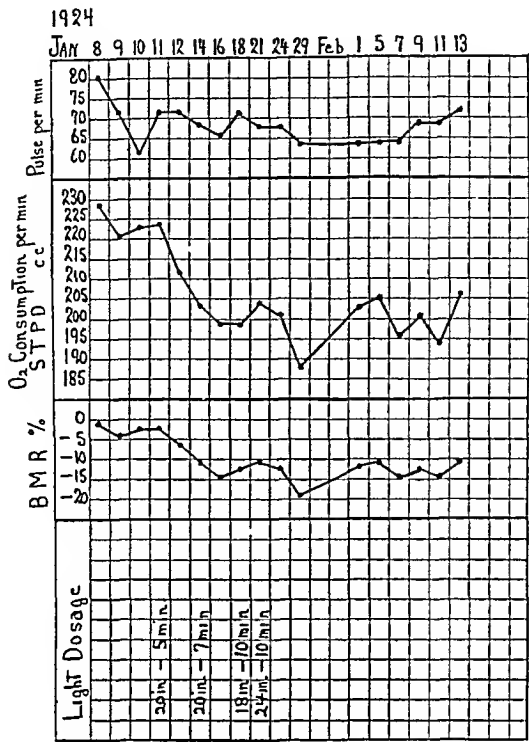


Chart 2 (case 2) —Effect of ultraviolet light on patient with tertiary syphilis and aneurysm of the arch of the aorta

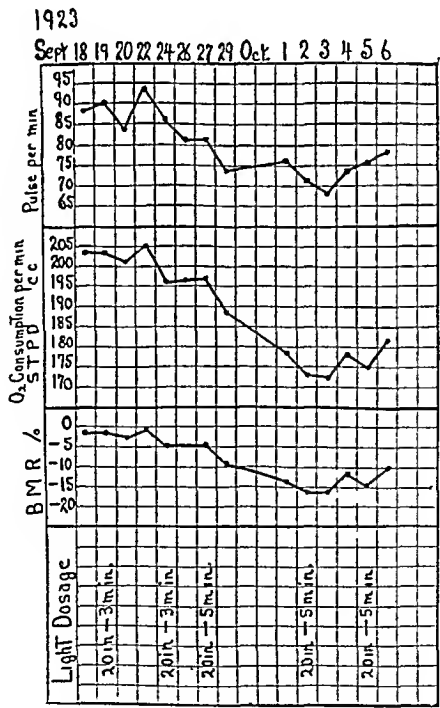


Chart 3 (case 3) —Effect of ultraviolet light on a patient with chronic pelvic infection

the decrease in heat production varied from 13 to 16 per cent Those who received only two light exposures (experiments 4 and 5, charts 4 and 5), resulting in slight pigmentation, showed less decrease of heat production, 7.8 and 10.5 per cent, respectively The pulse rate varied directly as the level of the total metabolism

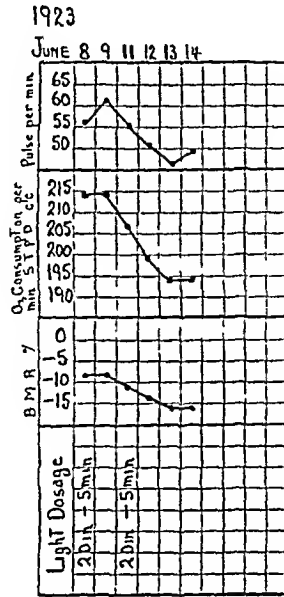


Chart 4 (case 4) —Effect of ultraviolet light on patient with myocarditis

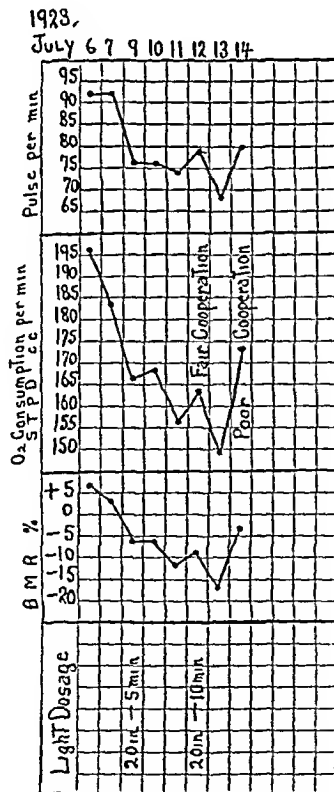


Chart 5 (case 5) —Effect of ultraviolet light on patient with alveolar abscess

In experiments 1 and 2 (charts 1 and 2), the decreased oxygen consumption persisted to a varying degree for twenty-three days after the light exposures were stopped. It should be noted that the light exposures in experiments 4 and 5 (charts 4 and 5) were at 20 inches (50.8 cm) distance, which might account for the rapidity with which the oxygen consumption became decreased. The increased oxygen consumption, July 12 and 14 (experiment 5, chart 5), was probably due to the poor cooperation of the patient.

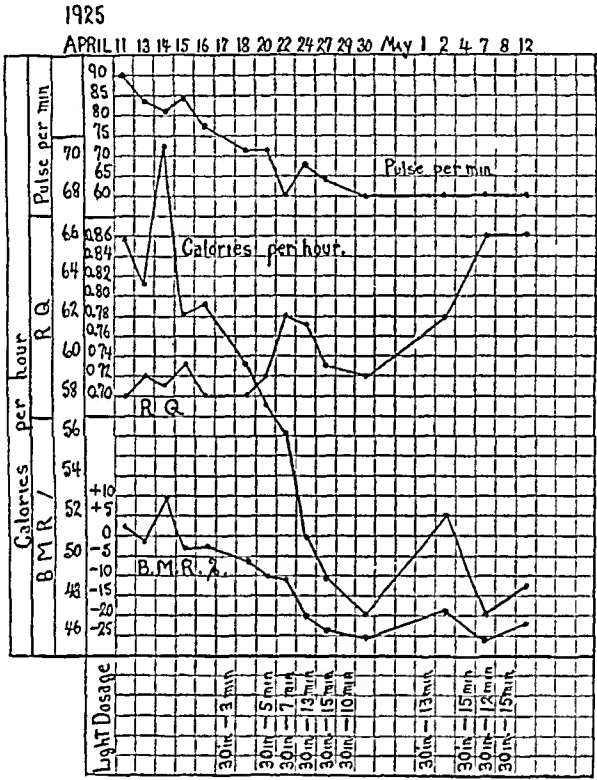


Chart 6 (case 6) —Effect of ultraviolet light on patient with pernicious anemia

*Group II*—Two types of cases that have an increased quantity of circulating bilirubin have been studied, namely, pernicious anemia and catarrhal jaundice. This group includes three subjects, one suffering from the former disease (experiment 6, chart 6) and two from the latter (experiments 7 and 8, charts 7 and 8). In two of the cases, experiments 6 and 7, the decrease in heat production was marked, 24.1 and 24.5 per cent, respectively. In experiment 8 the decrease was 8 per cent. The fall in pulse rate paralleled the lowering of the total metabolism. It would appear that the increased amount of circulating bilirubin rendered these patients especially sensitive to ultraviolet light, for the lowering of heat production preceded the development of marked pigmentation.

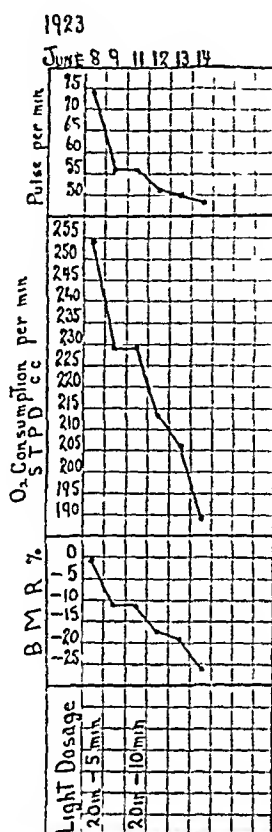


Chart 7 (case 7) —Effect of ultraviolet light on patient with catarrhal jaundice

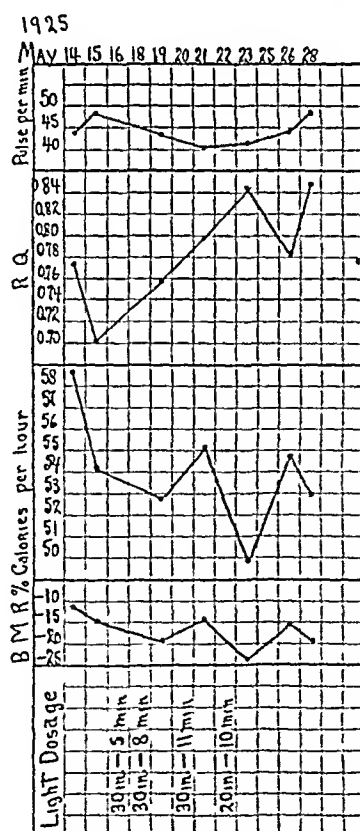


Chart 8 (case 8) —Effect of ultraviolet light on patient with catarrhal jaundice

*Negative Results*—Of the ten patients studied, it was stated that two failed to develop a lowered heat production after an extended period of light exposures. One was a boy, aged 15 years, who was convalescing from bilateral pleurisy with effusion. Twelve light exposures were given over a period of twenty-one days. Marked generalized pigmentation developed, but no appreciable change in heat production followed. Before the light exposures the basal metabolic rate varied from  $-0.5$  to  $-3.7$  per cent. During the light exposure the lowest result obtained was  $-11.7$  per cent, while at the end of the period the basal metabolic rate was  $-9.4$  per cent. It should be noted that the average pulse rate

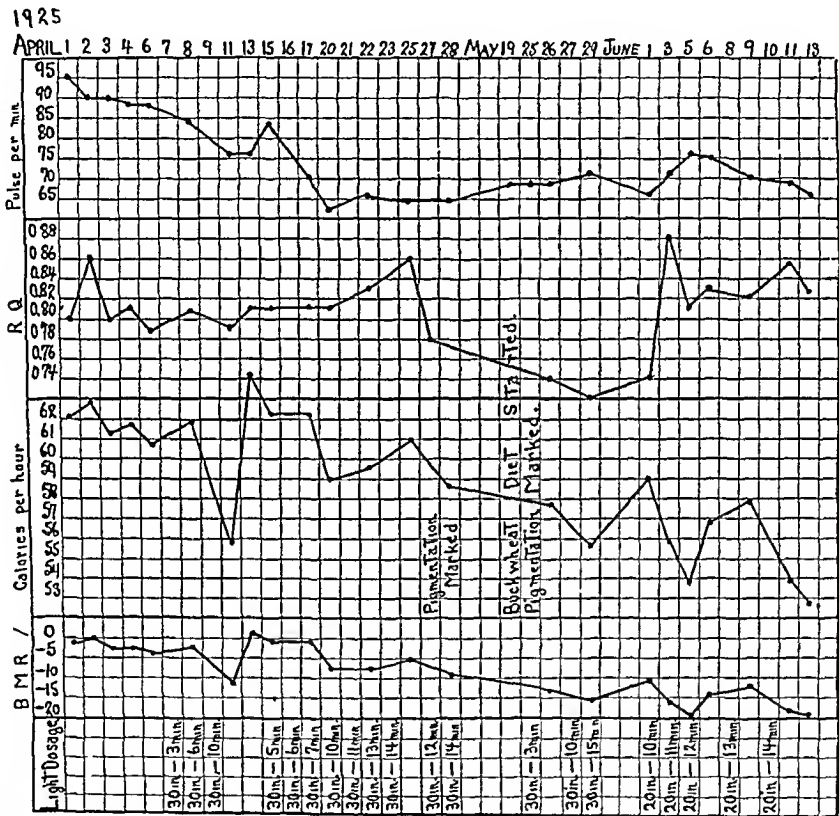


Chart 9 (case 9) —Effect of ultraviolet light on patient with fibrinous pleurisy with effusion (Convalescent)

became much slower. The fluctuations of the patient's total metabolism were considered to fall within physiologic limits. The data relating to this case are given in chart 9, and cover the period from April 1 to 28, 1925.

The other patient who failed to show a significant lowering of total metabolism after protracted ultraviolet light exposures was one with pernicious anemia. An increased amount of circulating bilirubin was present, as shown by a positive indirect van den Bergh reaction on the blood. Eight light exposures were given over a period of eighteen days.

Marked pigmentation did not develop. Prior to the light exposures the basal metabolic rate on five occasions varied from —13.1 to —14.5 per cent. After the exposures were started, the lowest basal metabolic rate, —18.6 per cent, was found on the third day. Subsequently the rate varied from —5.9 to —14.7 per cent. The results were not considered definite. In this case it is noteworthy that the average pulse rate did not appreciably change. The data are shown in chart 10.

#### SHORT PERIOD OBSERVATIONS

Since the metabolism determinations were made twenty-four hours or more after the light exposures, an attempt was made to determine

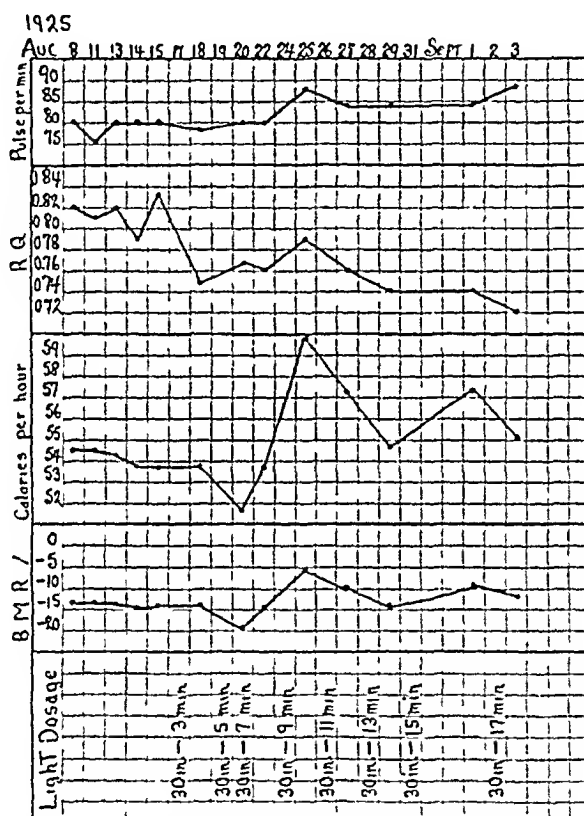


Chart 10 (case 10) —Effect of ultraviolet light on patient with pernicious anemia

whether there was an early change in consumption of oxygen. After obtaining a constant metabolism on consecutive days, a maximum light exposure was given. This was preceded by an oxygen consumption determination, which was repeated one and two hours afterward. In six experiments of this type on four patients, there was a slight rise in the heat production in five instances, the maximum being reached during the second hour. However, the hourly variations were so slight that they hardly fell without the experimental error. There was no change in the pulse rate. These data are recorded in the accompanying table.

The results in these short period observations may be contrasted with those reported by Harris<sup>1</sup> on rats. They differ fundamentally, however, in the fact that he used filtered irradiations, exposing the rats to pure ultraviolet light, while we used the total rays from a quartz mercury vapor lamp. The increase in carbon dioxide production as found by Harris lasted for thirty minutes only, while our experiments were conducted one and two hours after the light exposures.

### "SENSITIZATION" WITH BUCKWHEAT

Since buckwheat, due to its phytoporphyrin content, is capable of photosensitizing animals and human beings, an experiment was planned to determine whether a normal person who failed to show a lowering of the total metabolism after multiple ultraviolet light exposures would show any change in heat production after the introduction of an

#### *Short Period Observation*

Experiment	Diagnosis	Date	Light Dosage General Exposure Back and Front	Oxygen Consumption Cc per Minute S T P D			Basal Metabolic Rate, per Cent		
				Before	1 Hour	2 Hours	Before	1 Hour	2 Hours
11 Man Age, 32	Small medias- tinal tumor	1924 2/25	30 inches, 5 minutes	197.7			-6.9		
		2/26		193.2	199.7	200.0	-8.6	-5.6	-5.3
		2/27		210.9			-2.3		
12 Man Age, 25	Duodenal ulcer	3/5	30 inches, 10 minutes	194.0			-6.6		
		3/6		193.2	192.2	207.0	-6.9	-5.3	-0.2
13 Man Age, 56	Pleurisy with effu- sion (con- valescent)	3/8	30 inches, 9 minutes	201.0			+6.4		
		3/10		190.8	287.8	205.3	+0.8	-0.8	+8.5
		3/18		188.3	189.1	194.3	+0.0	+0.3	+2.9
14 Man Age, 22	Pleurisy with effusion (convalescent)	2/19	30 inches, 5 minutes	209.0			-8.4		
		2/21		207.1			-8.9		
		2/22		207.2	215.4	229.7	-9.9	-6.6	+0.0
		2/23		218.3			-5.1		
		2/25		220.7	214.4	224.1	-4.6	-7.3	-3.0
		2/26	30 inches, 10 minutes	217.8			-6.8		

extremely high buckwheat diet. The subject reported in experiment 9, chart 9, was chosen, as he had failed to develop a decreased total metabolism after twelve light exposures and the development of extreme pigmentation.

In chart 9 it will be seen that the high buckwheat diet was started on May 19. Its total values were protein 71 Gm, fat 90 Gm and carbohydrate 310 Gm, making 2,399 calories. Of this the buckwheat alone accounted for protein 10 Gm, fat 3 Gm and carbohydrate 107 Gm. The marked pigmentation that had developed by April 28 persisted. Ultraviolet light exposures were reinstituted on May 25. Subsequently, there was a definite fall in the total metabolism, the maximum lowering being obtained on the twenty-fifth day after the buckwheat diet was

started During this interval eight light exposures were given At no time did the patient suffer from toxic symptoms or skin manifestations, and his weight increased progressively

#### PROTOCOL

CASE 1—A man, aged 56, had fibrinous pleurisy (convalescent) The temperature was normal, and he had no jaundice The red blood cells totaled 3,550,000, the hemoglobin content was 70 per cent The basal metabolism was standardized before the light exposures were started, the basal metabolic rate fell 13.8 per cent Marked pigmentation developed The oxygen consumption remained lowered for twenty days after the light exposures were stopped The decrease in the average pulse rate should be noted

CASE 2—A man, aged 49, had tertiary syphilis, with aneurysm of the arch of the aorta The temperature was normal, and he had no jaundice The red blood cells totaled 5,100,000, the hemoglobin content was 80 per cent The basal metabolism was standardized before the light exposures were started The maximum decrease of the basal metabolic rate was 15.6 per cent Marked pigmentation developed The tendency for a slower pulse rate should be noted

CASE 3—A woman, aged 36, had a chronic pelvic infection (gonorrhea) The temperature was normal, and she did not have jaundice The red blood cells totaled 3,490,000, the hemoglobin content was 75 per cent The basal metabolism was standardized before the light exposures were started The oxygen consumption was not affected until after the third light dosage The maximum lowering was 14.5 per cent Marked pigmentation developed The slower pulse rate should be noted

#### SUMMARY OF BLOOD COUNTS

	Red Blood Cells	White Blood Cells	Hemoglobin (Haldane) Per Cent
April 13, 1925	1,210,000	4,200	—
April 18, 1925	1,390,000	2,800	29
April 29, 1925	2,300,000	3,200	46
May 8, 1925	2,290,000	4,600	54

CASE 4—A man, aged 58, had myocarditis The temperature was normal, and there was no jaundice The red blood cells totaled 4,910,000, the hemoglobin content was 85 per cent Satisfactory standardization was not made before the light exposures were started There was a definite lowering of the oxygen consumption Pigmentation of the skin which developed was slight We were unable to continue the work further

CASE 5—A woman, aged 19, had an alveolar abscess The temperature was normal, and jaundice was not present The red blood cells totaled 5,000,000, the hemoglobin content was 90 per cent Satisfactory standardization was not accomplished before the light exposures were started, but there was a definite decrease in oxygen consumption Only slight pigmentation developed Because of poor cooperation on July 12 and 14, the results on those days are not reliable

CASE 6—A man, aged 41, had pernicious anemia The van den Bergh test on the blood gave a negative direct reaction and a positive indirect reaction There was no bile pigment in the urine The basal metabolism was standardized before the light exposures were started The maximum lowering of the basal metabolic rate was 24.1 per cent A marked reduction in the total metabolism occurred, April 24, before pigmentation had developed At no time was pigmentation marked The lowering of the pulse rate should be noted The increased respiratory quotient indicates a greater percentage of combustion of carbohydrate as the total metabolism falls

CASE 7—A man, aged 29, had catarrhal jaundice. The visible jaundice was moderate, and there was a little bile pigment in the urine. The red blood cells totaled 5,350,000, the hemoglobin content was 85 per cent. The temperature was normal. Satisfactory standardization was not accomplished before the light exposures were started. The definite lowering in the oxygen consumption associated with a slower pulse rate after the second light exposure should be noted. Pigmentation was just commencing. We were unable to continue the work further.

CASE 8—A man, aged 24, had catarrhal jaundice, with bile pigment in the urine. The van den Bergh test on the blood gave a positive direct and indirect reaction. The blood cells totaled 4,550,000, the hemoglobin content was 90 per cent. The temperature was normal. The results show a moderate decrease in the basal metabolic rate without any change in the pulse rate. The pigmentation from the light exposures was definite.

CASE 9—A boy, aged 15, had fibrinous pleurisy with effusion, bilateral (convalescent). The temperature was normal, and jaundice was not present. After twelve light exposures, there was no significant decrease in the total metabolism, but the pulse rate was definitely slower. The pigmentation was definite. On May 19, the diet high in buckwheat values was started. Light exposures were reinstituted on May 25, with a subsequent fall in the basal metabolic rate to minus 21 per cent. There was no further change in the pulse rate.

CASE 10—A man, aged 36, had pernicious anemia. The van den Bergh test on the blood gave a negative direct and a faintly positive indirect reaction. There was no bile pigment in the urine. After eight light exposures, there was no significant decrease in the basal metabolic rate, and the pulse rate remained unchanged. Pigmentation was moderate after the light exposures.

#### COMMENT

The results reported show that the rays from a quartz mercury vapor lamp are capable of causing an appreciable reduction in the total metabolism in certain persons. This physiologic action is more pronounced when there is an excess of bilirubin circulating in the blood stream. The same phenomenon has been produced by an excessive consumption of buckwheat, presumably due to absorption of phytoporphyrin. If Harris' theory of the mechanism of sensitization of an animal rendered photosensitive is correct, one would expect that the marked skin pigmentation that was present would have neutralized the effect of the ultraviolet light. It might be that phytoporphyrin acted in the same way as bilirubin, in support of this theory is the fact that both are fluorescent substances. In persons in whom these materials have not been present a more marked pigmentation of the skin has been essential in obtaining a lowering of the total metabolism, and in such instances the decrease has not been as marked. This lowering of the metabolism is not transitory.

The most logical explanation of this phenomenon from known facts depends on our knowledge of the action of melanin in the skin. It has been observed by Harris<sup>1</sup> that by raising the external temperature there is a greater drop in the carbon dioxide production over short time experiments in black rats than in white ones. The same observation was obtained in rats exposed to the total rays from a quartz mercury

vapor lamp and from pure ultraviolet rays alone (wave length, from 291 to 436 millimicrons) In the latter cases, the extra lowering due to pigment amounted to 16.8 and 16.3 per cent, respectively Harris also has proved that pigment causes the skin to become hotter at a given external temperature Apparently melanin is able to degrade the ultraviolet rays into heat rays Thus, by supplying heat from solar energy to the tissues, the subject's oxygen consumption falls

This theory is supported by the fact that melanin is a fluorescent substance, and plant physiologists have found that such substances can convert short into longer light waves It is probable that bilirubin and phytoporphyrin act in the same manner Further, the most marked lowering of oxygen consumption in cases in which abnormal fluorescent substances are absent depends on an abundant pigmentation of the skin

#### CONCLUSIONS

Ultraviolet light from a quartz mercury vapor lamp is capable of lowering the total metabolism of certain persons Its effect is most marked when there is an increased amount of bilirubin circulating in the blood stream

Buckwheat, probably through the medium of phytoporphyrin, can produce a fall in total metabolism after ultraviolet light exposure

Radiant energy is most likely a new factor in the control of our level of total metabolism

# CARBOHYDRATE TOLERANCE IN NORMAL PERSONS AND IN NONDIABETIC PATIENTS

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AND

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Since the pioneer work of Jacobsen <sup>1</sup> in studying the fluctuations in blood sugar levels following various types of meals, the general subject of carbohydrate metabolism has been the subject of many investigations. We shall not here attempt a proper consideration and evaluation of every published research and clinical comment, since there are a number of articles in which this service has been attempted, and a reference to the important features of these may for the present suffice.

The article of Folin and Berglund <sup>2</sup> contains an excellent review of the general subject of carbohydrate metabolism from the point of view of the physiologic chemist. These authors conclude that the concept of renal threshold is absolutely true. They feel that the "glycuresis" described by Benedict, which, in brief, consists of readily demonstrable increases in sugar elimination too slight to give positive qualitative tests, is due to the excretion of nonutilizable carbohydrate bodies, and is independent of the blood sugar concentration. The blood sugar level was not elevated above the threshold by dextrose by mouth in quantities up to 200 Gm. The comments of Benedict <sup>3</sup> on this article serve to point out certain features that render doubtful some of the conclusions reached by Folin and Berglund. He feels that Folin and Berglund were not sufficiently careful in interpreting their data, and that their patients did show glycuresis after glucose feeding. He feels that the renal threshold may be wholly an artefact, and suggests that the elimination of sugar may be due to the presence in the blood of sugar having a chemical or physical structure differing from the utilizable blood dextrose.

Gray <sup>4</sup> has compiled from the literature the results of more than 900 tolerance tests. From the observations on 300 persons who were considered normal and who received the usual test load of 100 Gm of dextrose, he has constructed a composite curve which shows that the average fasting value is about 90, and that the average peak is about 140 at thirty minutes following the meal. The curve returns to the

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1 Jacobsen, A. T. B. *Biochem Ztschr* **119** 21, 1913

2 Folin, O., and Berglund, H. *J Biol Chem* **41** 213, 1920

3 Benedict, S. R., and Osterberg, E. *J Biol Chem* **55** 769 (April) 1923

4 Gray, Horace. *Blood Sugar Standards in Normal and Diabetic Persons*, *Arch Int Med* **31** 241 (Feb) 1923

fasting level at the end of three hours. Individual instances of high values were notable. There were values up to 160 for the fasting level, 280 for the peak, and 170 at the end of three hours. Of the three hour values, 41 per cent were above the fasting level. Of 129 cases in this group in which a urine examination was recorded, glycosuria was noted in 40 per cent. Curves obtained following the ingestion of from 25 to 200 Gm of dextrose do not, Gray finds, show greater variation than do individual curves on the same test load. The possibility that the tolerance of patients with even mild diabetes may be injured by test loads of 100 Gm of dextrose leads Gray to recommend that a test meal of two shredded wheat biscuits and 3 ounces (90 cc) of milk be used, at least as a preliminary test.

Mosenthal<sup>5</sup> feels that the use of a definite test load of 100 Gm of dextrose for all adults—no proportionment of the load to the weight of the patient being made—is entirely satisfactory. He feels that although every definite case of diabetes gives a high prolonged curve, abnormal curves are found in a wide variety of conditions and even in normal people. He believes that there are many people with diminished tolerance who are not prediabetic.

John<sup>6</sup> has published two articles reporting 200 consecutive carbohydrate tolerance tests in which 100 Gm of dextrose and a constant chemical technic were used. John's second article summarizes a number of articles bearing on this subject. He concludes that the most significantly abnormal feature of tolerance test curves is a prolongation, that is, a delayed peak, and a failure of the blood sugar concentration to return to the fasting level within three hours. The absolute height of the curve has little significance. He believes that lack of absorption from the intestine as the cause of a delayed rise is not important clinically. He feels that the renal threshold varies widely in different persons and is often lower than the commonly accepted value of 160 to 180 mg.

The research here reported was inspired by the opinion held by Gray and others that a test meal of 100 Gm of dextrose might do harm to a diabetic patient and that a starch meal might best be used, at least as a preliminary. Gray's suggestion of using two shredded wheat biscuits and 3 ounces of milk as a test meal appealed to us because of (1) its near approach to the usual American breakfast and (2) its ready availability. We were, however, unable to find in the literature any record of curves obtained in normal persons following this meal, or any comparison of curves obtained with this meal with those obtained when the standard test load of 100 Gm of dextrose was given to the same persons. We therefore determined to study a series of normal

5 Mosenthal, H. O. *M. Clin. N. Amer.* 9:549 (Nov.) 1925.

6 John, H. J. *J. Metab. Research* 1:497 (April) 1922, *ibid.* 4:255, 1923.

and nondiabetic persons with both types of test meal in order that we might contribute to the establishment of normal standards for the meal proposed by Gray, and at the same time establish a definite basis for the comparison of results by the two methods. At first we also planned to use the intravenous injection of 0.33 Gm of dextrose per kilogram of body weight as proposed by Rigler and Ulrich,<sup>7</sup> and so help to establish a basis of comparison for all three, but after a study of four cases we discontinued this portion of the work. The publication by Benedict<sup>8</sup> of a new method for the estimation of blood sugar which resembles closely the Folin-Wu method afforded the opportunity of making the duplicate analyses by the new method, and thus of determining whether or not values obtained by the two methods are directly comparable. As the work progressed, our interest in the phenomenon of glycosis and dextrose threshold prompted us to include a determination of the "sugar" in each sample of urine to determine whether any contribution could be made to an understanding of these important problems.

#### EXPERIMENTS

All subjects presented themselves in the morning without having eaten since the preceding dinner. Samples of blood were drawn before the test meal, and thirty minutes, ninety minutes and one hundred and fifty minutes after the completion of the test meal. These are the intervals we have been accustomed to use for tolerance tests. We have felt that they provide the maximum information with the fewest venipunctures and the minimum expenditure of time. Following the intravenous injection of dextrose, blood samples were drawn after ten minutes, forty minutes, seventy minutes and one hundred and thirty minutes. A specimen of urine was secured either immediately before or immediately after each sample of blood was taken. The water intake was not controlled.

The shredded wheat meal was prepared by heating the milk which was added to the biscuits after they had been softened by pouring hot salted water over them. Prepared in this way, the meal is quite palatable, without this preparation, it is too dry. Sufficient dextrose solution for five tests was prepared by adding to 500 Gm of anhydrous dextrose, the juice of two or three lemons, 1 cc of syrupy phosphoric acid, and water to make 1,000 cc. The mixture was served cold. The dextrose injected intravenously was a 50 per cent solution prepared by Eli Lilly & Co. This solution was injected undiluted at such a rate that from eight to ten minutes were required for the injection.

The samples of blood were analyzed by the Folin-Wu method, and by Benedict's modification of this method. The values obtained by the Folin-Wu method were not corrected for the disproportionality of color, as has now been made possible by Oser and Kerr.<sup>9</sup> Technical assistance was used as an accessory only, all analyses were under the immediate direction of one of us (H.R.), who made all colorimetric readings. In the Benedict method, the final color reagent reacts with the cuprous oxide much more slowly than does that used by Folin and Wu. The directions of Benedict that at least six minutes be allowed for this reaction were found to be important. A glass bead dropped in each tube is of great value in both methods as an aid to mixing.

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7 Rigler, L. G., and Ulrich, H. L. Blood Sugar Reaction Following Intravenous Injection of Glucose, *Arch. Int. Med.* **32** 344 (Sept.) 1923.

8 Benedict, S. R. *J. Biol. Chem.* **64** 207 (May) 1925.

9 Oser, B. L., and Kerr, W. J. *J. Biol. Chem.* **67** 319 (Jan.) 1926.

The specimens of urine that did not react with Benedict's qualitative reagent were analyzed exactly as described by Folin and Berglund. Those which gave a slightly positive test were analyzed in the same way except that a greater dilution was used. The specimens that contained more than 0.25 per cent were analyzed with Benedict's quantitative reagent.

The data in table 1 include the blood sugar curves obtained in twenty normal persons following the ingestion of two shredded wheat biscuits and 3 ounces of milk, and in five nondiabetic patients whose carbohydrate tolerance was probably unaffected by the disease condition present. Chart 1 is a composite of the twenty-five curves and shows that the normal type of response is a mild elevation of the blood sugar thirty minutes after the meal, a mild but distinct depression below the fasting level (hypoglycemia) ninety minutes after the meal and a return nearly to the fasting condition one hundred and fifty minutes after the meal. Chart 2 is a composite of the curves of sixteen normal persons and four nondiabetic patients for whom curves were obtained following both the

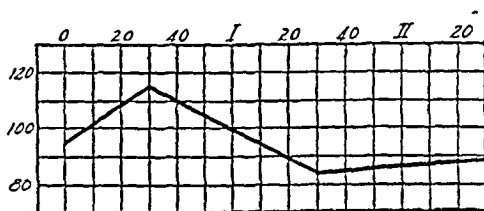


Chart 1—Composite curve from the observations on twenty normal persons and five nondiabetic patients who received two shredded wheat biscuits and 3 ounces of milk.

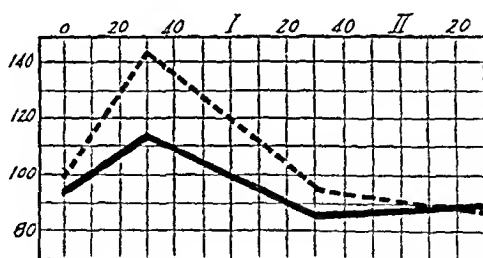


Chart 2—Composite curves from the observations on sixteen normal persons and four nondiabetic patients who received both test meals. Solid line shows response to meal of two shredded wheat biscuits and 3 ounces of milk, broken line, response to meal of 100 Gm of dextrose.

shredded wheat and dextrose meals, the data for which also appear in table 1. The elevation of the blood sugar observed thirty minutes after the starch meal is about one half that found after the dextrose meal. The hypoglycemia that follows the dextrose meal is less marked at ninety minutes and more marked at one hundred and fifty minutes than that which followed the shredded wheat meal. Compared with the composite curve given by Gray, our composite curve shows the following features: (1) Our curve starts at 98 instead of 90, (2) the peak is practically the

TABLE 1—Blood and Urine Analyses on Persons Studied After Starch and Dextrose Meals

Case	Sex	Age	Weight, Pounds	Height	Family History of Diabetes	Diagnosis	Two Shredded Wheat with 3 Ounces of Milk					100 Gm. of Dextrose					Type of Curve
							Data	Fasting	30 Min	90 Min	150 Min	Type of Curve	Fasting	30 Min	90 Min	150 Min	
1	♀	24	123	5 feet 7 inches	Negative	Normal	A	92	83	75	88	Trace	94	120	87	82	Glycuresis
							B	84	78	71	84		82	113	84	81	
							C	—	Trace	Trace	Trace		0.071	0.015	0.012	0.066	
							D	—	—	—	—		—	0.038	0.025	0.018	
2	♀	31	126	5 feet 7½ inches	Negative	Normal	A	85	94	93	78	Trace	81	123	93	75	Glycuresis
							B	75	81	86	79		74	110	81	68	
							C	—	Trace	Trace	—		0.082	0.056	0.042	0.122	
							D	—	—	—	—		0.013	0.038	0.037		
3	♂	26	138	5 feet 11 inches	Negative	Acne vulgaris	A	89	112	54	78	Trace	84	178	72	55	No glycuresis
							B	80	100	51	67		79	153	66	53	
							C	—	—	—	—		22	17	31	37	
							D	—	—	—	—		0.101	0.082	0.103	0.095	
4	♀	29	126	5 feet 7 inches	Negative	Hypothyroid controlled	A	86	103	82	85	Trace	77	110	69	77	No glycuresis
							B	75	95	71	79		74	93	60	74	
							C	—	—	—	—		—	—	—	—	
							D	—	—	—	—		—	—	—	—	
5	♂	41	188	6 feet 1 inch	Negative	Normal	A	86	97	92	82	Trace	98	154	80	78	Glycuresis
							B	—	—	—	—		92	154	72	72	
							C	20	75	100	230		25	40	90	72	
							D	0.039	0.037	0.008	0.009		0.033	0.037	0.007	0.013	
6	♂	30	118	5 feet 6 inches	Negative	Normal	A	104	110	88	95	Trace	90	124	76	78	Glycoursuria
							B	—	—	—	—		76	114	70	68	
							C	60	25	26	40		21	30	385	225	
							D	0.058	0.047	0.107	0.123		0.089	0.080	0.072	0.051	
7	♂	23	190	6 feet	Negative	Normal	A	88	118	63	85	Trace	100	168	73	64	Glycoursuria
							B	66	94	50	68		73	167	59	53	
							C	100	28	76	46		80	33	42	42	
							D	0.053	0.132	0.089	0.073		0.047	0.70	0.95	0.40	
8	♂	25	150	5 feet 10 inches	Negative	Normal	A	91	115	84	93	Trace	89	141	124	103	Doubtful
							B	74	94	67	72		76	115	95	84	
							C	40	41	54	49		24	24	42	22	
							D	0.106	0.104	0.122	0.100		0.073	0.065	0.084	0.112	
							E	—	0.086	0.066	0.040		—	0.031	0.035	0.025	

9	♀	20		Negative	Normal	A B C D E	99 81 0 045	109 85 0 107 0 072	87 69 0 109 0 033	96 70 0 090 0 077	Doubtful glycuresis	92 81 0 027	167 131 0 013 0 025	116 100 0 018 0 023	92 81 0 032 0 011	No glycuresis
10	♂	29	132	5 feet 5 inches	Normal	A B C D E	105 83 88 0 076	114 92 68 0 053 0 072	64 57 28 0 039 0 028	92 78 29 0 090 0 026	Glycuresis	97 87 38 0 067	152 140 35 0 063 0 044	101 93 49 0 072 0 035	96 81 150 0 015 0 023	Glycuresis
11	♂	38	140	5 feet 5½ inches	Achyia	A B C D E	100 76 134 0 068	125 89 76 0 034 0 032	85 61 38 0 128 0 039	90 73 30 0 117 0 035	Glycuresis	111 93 20 0 117	144 120 22 0 189 0 084	112 99 30 0 101 0 030	96 82 27 0 101 0 027	Glycuresis
12	♂	41	145	5 feet 8¼ inches	Negative	A B C D E	83 77 42 0 109	97 92 36 0 110 0 078	73 66 33 0 123 0 011	71 70 41 0 038 0 040	Glycuresis	109 89 55 0 096	119 95 30 0 114 0 068	87 91 23 0 179 0 070	72 55 24 0 220 0 053	Glycuresis
13	♂	22	135	5 feet 10 inches	Positive	A B C D E	105 72 0 105	115 88 0 061	93 66 0 061	86 60 0 015	Glycosuria	110 84 0 110	111 119 77 0 040 0 076	92 80 39 0 176	105 86 45 0 117	Glycosuria
14	♂	28	145	5 feet 5 inches	Positive	A B C D E	113 82 0 085	152 111 0 086 0 092	90 69 0 073 0 062	93 63 0 017 0 032	Glycuresis	94 83 130 0 028 0 022	167 153 41 0 174 0 142	107 97 253 0 100 0 253	82 74 97 0 020 0 028	Glycosuria
15	♂	30	140	5 feet 10 inches	Positive	A B C D E	104 95 66 0 032	125 112 25 0 060 0 048	111 97 31 0 060 0 035	106 97 0 063 0 031	Glycuresis	100 84 0 109	111 84 0 118 0 078	88 70 0 151 0 013	91 80 0 117 0 046	Glycuresis
16	♂	26	135	5 feet 8 inches	Positive	A B C D E	105 89 77 0 038	140 113 69 0 032 0 126	85 75 62 0 288 0 139	96 84 77 0 067 0 052	Doubtful	130 105 22 0 087	149 129 19 0 075 0 028	101 87 30 0 116 0 044	91 84 33 0 146 0 018	Doubtful
17	♂	40	180	5 feet 9 inches	Positive(?)	A B C D E	96 81 50 0 110	145 110 19 0 114 0 044	99 82 17 0 107 0 050	95 80 29 0 112 0 032	Glycuresis	110 84 99 0 086	165 123 25 0 112 0 036	150 112 26 0 170 0 039	134 162 27 0 149 0 010	Glycuresis

TABLE 1.—*Blood and Urine Analyses on Persons Studied After Starch and Dextrose Meals*¹—*Continued*

Case	Sex†	Age	Weight, Pounds	Height	Family History of Diabetes	Diagnosis	Two Shredded Wheat with 3 Ounces of Milk					100 Gm. of Dextrose					Type of Curve
							Date	Fasting	30 Min	90 Min	150 Min	Type of Curve	Fasting	30 Min	90 Min	150 Min	
18	♂	22	145	5 feet 7 inches	Negative	Normal	A B C D E	84 77 32 0 122	94 84 218	81 75 0 182	86 77 23 0 139 0 035	No glycosuria	96 79 65 0 080	124 93 18 0 094 0 034	108 84 28 0 122 0 034	80 67 19 0 186 0 035	No glycosuria
19	♂	22	135	5 feet 5 inches	Negative	Normal	A B C D E	90 71 48 0 115	136 97 17 0 144 0 048	108 81 19 0 209 0 010	95 79 17 0 198 0 034	Glycosuria	109 96 28 0 086 0 048	156 128 21 0 381 0 169	95 84 110 0 197 0 217	119 108 31 0 117 0 036	Glycosuria
20	♂	21½	145	5 feet 6 inches	Negative	Normal	A B C D E	90 76 21	113 96 11	107 91 195	100 88 17	No glycosuria	96 81 40 0 075	139 110 54 0 040	80 72 136 0 030	82 79 62 0 036	No glycosuria
21	♂	22	145	5 feet 6 inches	Positive	Normal	A B C D E	102 92 98 0 075	113 100 49 0 075	78 72 42 0 122 0 051	81 80 50 0 080 0 040	Glycosuria	96 81 40 0 075 0 044	139 110 54 0 040 0 014	80 72 136 0 030 0 011	82 79 62 0 036 0 035	No glycosuria
22	♂	21	176	6 feet 1 inch	Positive	Normal	A B C D E	85 72 11 0 102 0 021	102 94 14 0 078 0 022	69 64 33 0 102 0 034	84 71 53 0 057 0 030	No glycosuria	91 76 80 0 120	134 110 31 0 048	102 98 18 0 112 0 538	100 92 34 0 126 0 043	Glycosuria
23	♂	29	160	5 feet 10 inches	Negative	Auricular fibrillation	A B C D E	100 88 20 0 034	107 91 11 0 074	83 75 37 0 087	95 84 40 0 067 0 027	No glycosuria	89 82 285 0 028	146 113 17 0 011 0 031	114 106 35 0 035 0 034	114 96 110 0 136 0 043	Doubtful
24	♂	22	135	5 feet 1 inch	Negative	Normal	A B C D E	83 77 40 0 112 0 024	122 110 16 0 115 0 036	70 63 28 0 141 0 040	88 77 53 0 062 0 034	Glycosuria	89 75 110 0 080	158 141 96 0 442 0 194	132 115 46 0 412 0 203	128 107 37 0 368 0 136	Glycosuria
25	♂	24	163	5 feet 9 inches	Negative	Normal	A B C D E	98 77 52 0 012 0 023	125 102 16 0 014 0 023	87 76 33 0 040	77 71 29 0 027 0 027	Glycosuria	96 100 100 0 063	156 141 34 0 078 0 054	121 106 42 0 111 0 047	122 106 52 0 088 0 046	Glycosuria

\* In this and table 2, A means blood sugar by the Fohn and Wu method, B, blood sugar by the Benedict method, C, volume of urine, D, urine sugar concentration, and E, urine sugar, grams per hour.  
† In this and table 2, ♂ indicates male, ♀, female.

same, and (3) our curve has returned to the fasting level within one and one-half hours, falling to 88 at two and one-half hours. Gray's curve returns to the fasting level in three hours, being distinctly above the fasting level at one and two hours.

Chart 3 is a composite from tables 1 and 2, showing the curves obtained following starch, dextrose and intravenous dextrose tests in the same four persons. With respect to the starch and dextrose meals, the average of the four does not differ materially from the average of the twenty. The intravenous injection of dextrose produces the maximum hyperglycemia immediately. Forty minutes following the injection, the hypoglycemia is well marked. The observations at seventy and one hundred and thirty minutes following the injection show a gradual return to the normal fasting blood sugar level. As compared with the other standard tests, the normal response to the injection of 0.33 Gm. of dex-

TABLE 2—*Blood and Urine Analyses on Persons Studied After Starch and Glucose Meals, and Glucose Intravenously*

Case	Sex	Age	Weight, Pounds	Height	Family History of Diabetes	Diagnosis	Data	Dextrose Intravenously, 0.33 Gm. per Kg.				
								Fast- ing	10 Min	40 Min	70 Min	130 Min
1	♀	24	128	5 feet 7 inches	Negative	Normal	A	94	212	59	80	88
							B	79	198	50	68	74
							C	—	50 cc	—	—	—
							D	—	0.5	0.1	—	—
							E	—	1.50	—	—	—
2	♀	31	126	5 feet 7½ inches	Negative	Normal	A	81	127	54	85	94
							B	72	110	47	79	87
							C	—	46 cc	—	—	—
							D	—	1.2	—	—	—
							E	—	3.30	—	—	—
3	♂	26	138	5 feet 11 inches	Negative	Acne vulgaris	A	96	205	109	74	91
							B	85	190	95	68	86
							C	—	35 cc	87 cc	—	—
							D	—	0.86	0.1	—	—
							E	—	1.80	0.52	—	—
4	♀	29	126	5 feet 7 inches	Negative	Hypo- thyroid controlled	A	91	166	72	96	88
							B	80	163	72	86	89
							C	—	30 cc	—	—	—
							D	—	0.82	—	—	—
							E	—	1.6	—	—	—

trose per kilogram of body weight would seem to be characterized by (1) greater fluctuations both above and below the normal fasting blood sugar level and (2) a shorter duration of the curve.

Chart 4 is a composite from table 1 of the curves obtained by giving 125 Gm. of dextrose to three persons and one nondiabetic patient. This curve is characterized by a lack of a hypoglycemia phase during the period of observation, the blood sugar remaining well above the fasting level at two and one-half hours.

The data regarding sugar elimination do not lend themselves to the construction of composite charts. The sugar elimination in grams per hour has been plotted on the individual charts of all the cases in which

the data were obtained. The values found for each sample of urine taken after the meal was given were regarded as an average for the preceding period, and the plotted points were therefore located in the middle of the period and not at the end. Two of the individual charts have been selected for publication as examples.

From a study of the graphs in eighteen cases with complete data, it appears that following the shredded wheat meal, glycuressis was absent in two, doubtful in two and rather definitely present in thirteen cases. Glycosuria was present in one case. We have applied the term glycuressis

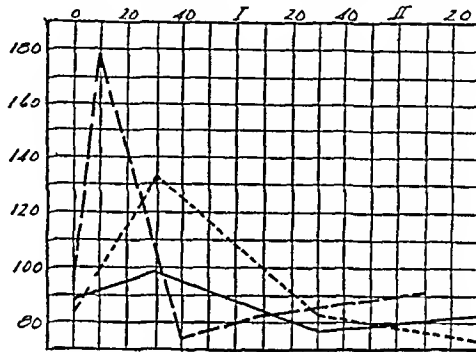


Chart 3—Composite curves from the observations on four persons who received both test meals and dextrose intravenously: solid line, response to meal of two shredded wheat biscuits and 3 ounces of milk, dotted line, response to meal of 100 Gm of dextrose, broken line, response to injection intravenously of 0.33 Gm of dextrose per kilogram of body weight.

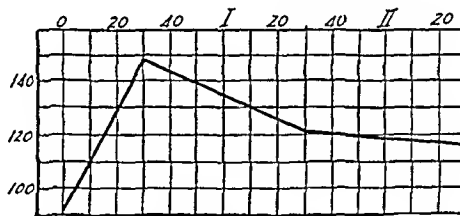


Chart 4—Composite curve from the observations on three normal persons and one nondiabetic patient who received meal of 125 Gm of dextrose.

to those curves which show from their form an increased elimination of sugar shortly after the test meal, provided that the rate of elimination was not greater than 90 mg an hour. We have assumed that the method used measures dextrose. Any such division of curves into types is, we realize, rather arbitrary, and therefore our decision in each instance has been indicated in table 1. In a few instances, the concentration of sugar in the urine was sufficient to give a positive qualitative test, but in no instance was the elimination of sugar appreciable. Following the dextrose meal, it appears that of nineteen cases in which the data are complete, four exhibited no glycuressis, two were doubtful, eight showed a fairly definite glycuressis and five showed an unmistakable glycosuria. There were no doubtful cases between the latter groups.

COMMENT

Carbohydrate tolerance tests as performed in clinical medicine give curves that are only fragmentary and approximate records of the fluctuations in blood sugar concentration. The true curve is, of course, a smooth and not a broken one. To obtain the true curve, samples of blood would have to be taken perhaps as frequently as every five minutes during the first hour, when the blood sugar is changing rapidly. Such a procedure is not practicable, nor would the results, so far as we know, be of greater value clinically. All so-called low curves should, however,

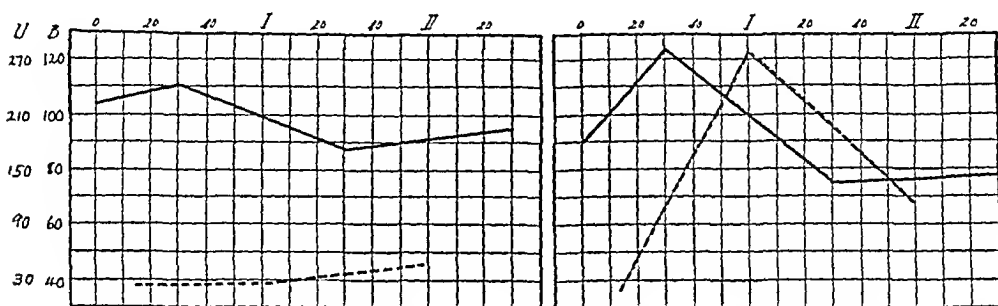


Chart 5—Individual chart of patient 6, a woman, aged 30, showing method of study, the patient was 66 inches in height and weighed 118 pounds (53.5 Kg). Left: doubtful condition following two shredded wheats and 3 ounces of milk, right: glycosuria following 100 Gm of dextrose.

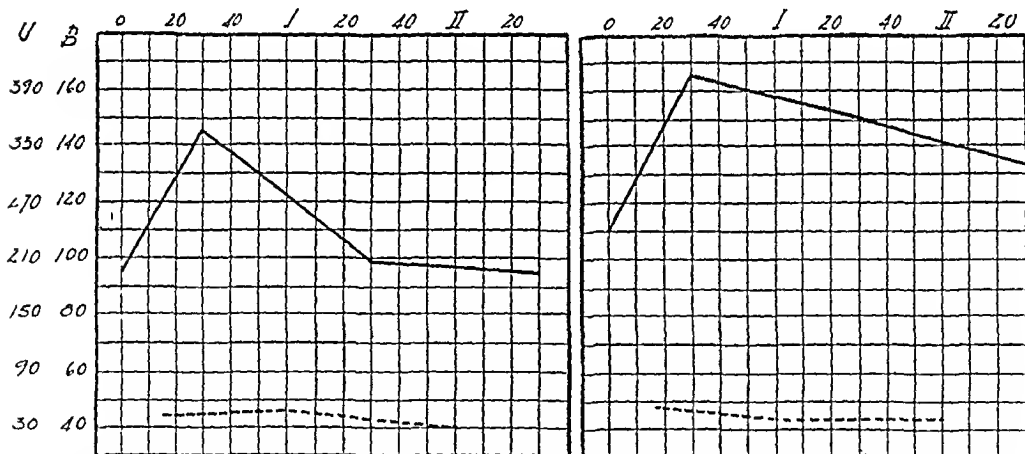


Chart 6—Individual chart of patient 17, a man, aged 30, showing method of study, the patient was 69 inches in height and weighed 180 pounds (81.6 Kg). Left: glycuresis following two shredded wheats and 3 ounces of milk, right: glycuresis following 100 Gm of dextrose.

be reexamined with several blood sugar estimations within the first hour to make sure they are not merely "shortened" curves. It has been found that the maximum rise in blood sugar concentration following the ingestion of 100 Gm of dextrose by normal persons usually occurs between fifteen and forty-five minutes following the meal, hence, a blood sample taken at thirty minutes will usually record a value near the maximum. In individual cases, however, the difference may be

considerable All experimental studies on renal threshold should include sufficiently frequent estimations of blood sugar to determine with reasonable exactness the maximum blood sugar concentration

The comparison between the curves obtained with test meals of both shredded wheat and dextrose shows that the general shape of the curves is the same in both The rise in blood sugar concentration is greater following the dextrose meal, and this will usually result in a higher value at the thirty minute interval The later appearance of hypoglycemia following the dextrose meal and the continued elevation of the blood sugar level at two and one-half hours in the patients that received 125 Gm of dextrose confirm the observations others<sup>10</sup> have made that increasing the load tends to prolong the curve

Since the length of time required for the blood sugar concentration to return to the fasting level is generally held to be the most important feature of the curves for the clinical diagnosis of diabetes, it would appear that those who would proportion the quantity of dextrose given to the weight of the patient have theoretical support for their view Weight is, however, usually an index of the state of nutrition of a person and not of the amount of glandular tissue present It is therefore probably better not to vary the load, unless a child or a person definitely larger or smaller than the average mold is being tested

It would also appear that the duration of the curve following any suggested test meal would have to be determined experimentally in a series of normal persons before the test could have clinical value If the shredded wheat meal is used, a consideration of our data indicates that the blood sugar concentration should return to the fasting level within two hours Even so, patient 17 shows a prolonged curve following the dextrose meal, and yet the blood sugar concentration fell to the fasting level within two hours following the shredded wheat meal It may be that this represents a difference in tolerance on different days Except for some nervousness and some difficulty with his studies, this man is apparently well He is a little overweight The family history of diabetes is questionable

We feel that the shredded wheat meal is a little too small for common use and that it could be improved by the addition of 50 Gm or so of dextrose or sucrose The amount of sugar added could be varied in proportion to the weight of the patient if desired, the carbohydrate content of the shredded wheat and milk being subtracted from the total calculated dose Such a test meal should give results directly comparable to those obtained with 100 Gm of dextrose and would be far more agreeable to the patient The 100 Gm dextrose makes a nauseating dose however disguised

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10 Jacobsen, Boe, Bergmark, Sakaguchi, Bailey, Shouse, MacLean, DeWes-selow and Spencer, cited by Gray (footnote 4)

The comparison of the results by the method of Folin and Wu and that of Benedict shows that they are comparable if one remembers that results by the Benedict method will average about 20 per cent lower than those of Folin and Wu (chart 5). Since the completion of our experimental work, Folin<sup>11</sup> has published an article criticizing Benedict's method and modifying the reagents of the Folin-Wu method so as to secure the advantages claimed by Benedict<sup>12</sup>. All this shows that the clinician should be slow to adopt new methods. A change should not be made unless there is some definite advantage to be gained. Time should be permitted for a careful critical review of the method by chemists of large experience in this field. Modern microchemical analytic methods, although vastly superior to those of preceding decades, are doubtless still far from perfect. For this reason, values obtained in blood analyses of various kinds should be interpreted after consideration of the method by which they were obtained.

The chief point of interest in the cases in which dextrose was given intravenously is the rapidity with which hypoglycemia appears, that is,

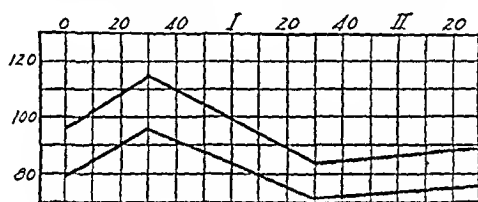


Chart 7—The upper curve is a composite of curves by the Folin-Wu method, the lower curve, a composite of curves by the Benedict method

within forty minutes in three of the four cases, and probably within forty-five or fifty minutes in the fourth case. The use of dextrose intravenously as a test substance was proposed when it was thought that irregularities in the absorption of dextrose, as described by Fitz, Beeler and Bryan,<sup>13</sup> might be a factor of considerable importance in the clinical application of the test. It is the opinion of John<sup>6</sup> and others that this factor is of little importance clinically, and there would appear to be little need for an intravenous test. The test load which most nearly approaches a normal meal, is, in our opinion, the best. The response of the patient to the ingestion of food is, after all, the important thing.

The large proportion of patients (52 per cent) who show glycosuria following the shredded wheat meal supports the opinion of Benedict that this is the usual occurrence. The response to the dextrose meal is even more interesting. If the study were confined to the four cases that showed no glycosuria, one would say that subthreshold hyper-

11 Folin, O. *J Biol Chem* **67** 357 (Feb) 1926

12 Benedict has now replied. *J Biol Chem* **48** 759 (June) 1926

13 Fitz, R., Beeler, C. L., and Bryan, A. W. *J Metab Research* **1** 549 (April) 1922

glycemia due to dextrose ingestion produces no glycuressis. A fairly definite subthreshold glycuressis is, however, observed in eight cases, two cases being regarded as doubtful. It may be that this comes from the complex carbohydrate present in the lemon juice or impurities in the sugar, but it seems more reasonable to us that the presence or absence of glycuressis is due to individual variation. Definite glycosuria was present in five cases. In one of these the highest observed blood sugar concentration was under 130, and in two it was over 160. It is our opinion, however, that the tolerance test, as designed for clinical work, does not provide sufficiently frequent observations to throw much light on the problem of renal threshold. The sharp separation of our cases which show glycuressis from those which show glycosuria seems to us to point to the existence of a definite renal threshold—that there is in each individual, at a given time, a certain blood sugar concentration at which the urine sugar concentration begins to mount rapidly as the blood sugar concentration rises.

#### SUMMARY AND CONCLUSIONS

In the response of twenty normal and five nondiabetic subjects to a meal of two shredded wheat biscuits and 3 ounces of milk, the average peak at thirty minutes was 142. The average duration was less than two hours. As compared with the average response given by these subjects and that of sixteen normal and four nondiabetic subjects to the shredded wheat meal and the usual 100 Gm of dextrose, the curve given by the former is flatter and of shorter duration. A consideration of these data indicates that the shredded wheat meal is a rather small load, and it is suggested that a combination of sugar and shredded wheat and milk be tried. Such a meal would appear to have the advantage of availability, palatability and near approach to an ordinary breakfast.

The average curve obtained in four persons given 125 Gm of dextrose, as compared with the average curve for those given 100 Gm, shows a greater elevation of the blood sugar level and a prolongation of the curve. This confirms the observation of others that an increase in the load tends to prolong the curve.

A study of sugar elimination in these subjects indicates the presence of glycuressis in many persons following both types of meal. The sharp demarcation between glycuressis and glycosuria suggests the presence of a definite renal threshold. The individual variation observed indicates the necessity of carrying out such studies on a sufficiently large number of subjects.

# BILIARY, PANCREATIC AND DUODENAL STUDIES

## II ESTIMATION OF PANCREATIC ENZYMES AND VALUE OF SUCH DETERMINATIONS FROM A CLINICAL STANDPOINT

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The functions of the pancreas will never be understood until there are methods for ascertaining its fundamental physiology. On this question a great deal of work is now being done. Of course, the function of the pancreas that is most obvious is the enzyme secretion. How to estimate it in some manner accurate enough for clinical investigation is the problem discussed in this article. There has been a great deal of study of the pure secretion, but that is of only academic help in the clinical problems.

A method of approach which will give a fairly faithful record of the functional state of the pancreas in its production of the so-called external enzymes is offered here. To begin with, an estimation was made of the amount of starch digested as shown in various dilutions of duodenal contents with the aid of iodine. Among the first to do this was Dr. Thomas R. Brown<sup>1</sup>. He made this estimation on the stools and specimens of urine, and was able to determine the diastase activities within fairly constant levels. It seemed only proper that some means of more accurately measuring the enzymic concentration should be developed. With this in mind, known quantities of sucrose which does not reduce Folin and Wu's alkaline copper sulphate solution were injected through a tube into the duodenum. At set intervals portions of the duodenal contents were removed and the amount of glucose obtained, as determined by its reduction of the above mentioned copper sulphate, was measured. This procedure was carried out in a series of cases until I was thoroughly convinced that although it is theoretically engaging, it is impracticable. After stimulating the pancreas with tenth normal hydrochloric acid and with a subsequent injection of the sucrose into the duodenum, the attempt was made. The sucrose was also used through the tube as stimulant enough of itself. Of course, in both cases pancreatic as well as bile flow was obtained, but there is little prospect of obtaining a fairly constant material in which the enzymes will act. At times, two or three readings that showed the desired upward curve were secured, but much more frequently the reductions were irregular in amount and

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<sup>1</sup> Brown, Thomas R. The Normal Amount of Diastatic Ferment in the Urine and Feces, and Its Variation in Diseases of the Pancreas, Tr. A. Am. Phys., 1914

frequently sterile Besides these disturbing factors, a sugar reducing substance in the bile itself usually strongest in the darkest, most concentrated portion was found at times

Consequently, the *in vitro* method was resorted to and followed through a fairly large number of cases, the last fifty of which are presented here At first different dilutions of the duodenal contents were tried with 1 cc of 1 per cent soluble starch using a buffer solution of  $p_H$  7.7 in both the dilution of the return fluid and the solution of starch Distilled water does not give satisfactory results, as will be shown below After considerable experimenting, it was found that the average duodenal contents gave satisfactory reductions in 1:600 dilution About seventy tests were made, using 1 cc of this dilution with 1 cc of the soluble starch solution A solution of 40 cc of 33 per cent magnesium sulphate warmed to body temperature and injected slowly through the tube into the bend of the duodenum was used as a stimulant Some patients become nauseated unless the process is performed slowly The sterile tube was taken by the patient after he had fasted over night It was practically always swallowed without the aid of water, but in the few cases in which it was thought advisable to give small quantities of water, it was removed by syringe as soon as the tube reached the stomach The patient then inclined on the right side, and the tube was allowed to drain into a beaker, while the bulb drifted slowly into the duodenum In this manner it was felt that the tube entered the desired spot without carrying a large supply of gastric contents with it It is not inferred, however, that none was constantly following the tube The position was carefully controlled by fluoroscope At times specimens of bile were obtained before it was certain that the tube was in place These were carefully separated and tested for enzymic activity I do not believe that this initial flow of bile before stimulation with magnesium sulphate represents a malfunction of the sphincter of Oddi When this initial flow ceased, stimulation was carried out as shown above After two minutes siphonage was instituted, and the bile was collected, great care being taken to collect aliquot portions of the so-called A, B and C bile into separate sterile tubes Until the flow became viscid, it was discarded as containing magnesium sulphate After thorough centrifugalization, dilutions of 1:600 were made of each of the three portions Often atypical returns were obtained, such as an entire absence of one of the component parts At times bile was not returned Into three sets of five tubes containing blood sugar were placed 1 cc, 0.8 cc, 0.6 cc, 0.4 cc, 0.2 cc of each fraction and made up to the total amount of 2 cc with 1 cc 1 per cent soluble starch and the necessary amount of  $p_H$  7.7 buffer The tubes were well shaken and placed in a water bath at 38 to 40 C for thirty minutes At this time 2 cc of alkaline copper

sulphate (Folin and Wu) were added to each tube, and the determinations were carried out in the manner suggested by the writers for the determination of blood sugar. The buffer solution was made according to Sorensen, as brought out by W. Mansfield Clark.<sup>2</sup>

An M/15 solution of primary potassium phosphate which contains 9.080 Gm  $\text{KH}_2\text{PO}_4$  in 1 liter of solution.

An M/15 solution of secondary sodium phosphate which contains 11.876 Gm  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  in 1 liter of solution.

Nine cubic centimeters of the secondary are added to 1 cc of the primary to make  $p_{\text{H}}$  7.731. The soluble starch solution must be well boiled and made up fresh every other day even when kept in the icebox. For the alkaline copper sulphate and the phosphomolybdic acid and the sugar standards, reference may be made to any number of sources. Stitt's<sup>3</sup> method was used in the present work.

For the determination of trypsin, the following method was used.

Three cubic centimeters 1:100 dilution of duodenal contents in buffer  $p_{\text{H}}$  7.7 is incubated in the water bath at 38 to 40 C with 2 cc 0.5 per cent purified casein in 0.3 per cent sodium carbonate. To this is added 5 cc each of 10 per cent sodium tungstate and two-thirds normal sulphuric acid. This is shaken well, put aside for two hours, filtered or centrifugalized and 5 cc of filtrate determined for nonprotein nitrogen by the nesslerization method of Folin and Wu (Stitt<sup>4</sup>).

For quantitative determination

**Diastase.** The reading in milligrams obtained in one tube is multiplied by 100 so as to be comparable with results obtained by smaller dilutions.

**Trypsin.** The reading in milligrams of nonprotein nitrogen obtained in one tube minus the reading for the control casein, the control duodenal contents being too low to give a color, is multiplied by 3 to ascertain the number of milligrams in the initial tube and by 50 for 100 cc of casein. The last multiplication is optional and used only to give a broader and more easily handled table for interpretation of results.

In order to eliminate as much as possible any action of ptyalin, all saliva was collected from the patient as he became conscious of it. Simultaneous estimations were made with it.

These methods are unwieldy and much too involved for clinical use. They have been used, however, in these cases in order to derive a basis for a simple and accurate method which is given below. In the intra-series comparison among the three sets of tubes it has never been possible to find any definite progression or increase in the amount of diastase. Usually the smallest reading is found in C, the highest in B and that found in A midway between the two. In all cases in which the greatest activity was found in A or C the reading in B was always of high enough activity to give a fair index of the pancreatic activity.

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<sup>2</sup> Clark, W. M. *Determination of Hydrogen Ions*, Baltimore, Williams & Wilkins Co., 1925.

<sup>3</sup> Stitt. *Practical Bacteriology, Blood Work and Parasitology*, ed 7, Philadelphia, P. Blakiston's Sons & Co., 1918.

TABLE 1—*Distase and Trypsin Found in Bile*

	Color	Quality	pH	Dias- tase	Tryp- sin		Color	Quality	pH	Dias- tase	Tryp- sin
1	A Yellow	Clear		66 64	12 50	26	A Yellow	Clear		71 66	
	B Dark	Clear		96 35	10 52		B Dark	Clear		66 14	
	O Light	Clear		76 80	5 28		O Yellow	Clear		71 66	
2	A Yellow	Clear	6 8	53 32		27	A Yellow	Clear		62 14	
	B Dark	Clear	4 6	36			B Dark	Clear		90 16	
	C Yellow	Clear	5 8	36 36			C Yellow	Turbid	100		
3	A Yellow	Clear		10 11		28	A Yellow	Clear		4 22	
	B Dark	Clear		6 25			B Dark	Clear		12 54	
	O Yellow	Turbid		0 0			O Yellow	Turbid		1 16	
3'	A Yellow	Clear	4 0	11 11		29	A Yellow	Clear			
	B Black	Clear	4 0	6 25			B Dark	Clear		62 0	
	C Yellow	Turbid	2 4	6 25			O Yellow	Turbid			
3''	A None					30	A Yellow	Clear			
	B Dark	Clear	7 0	6 04			B Black	Clear		57 62	
	O Yellow	Turbid	2 4	0 0			O Yellow	Clear			
4	A Yellow	Clear		33 33		31	A Yellow	Clear		30	
	B Amber	Clear		71 42			B Dark	Clear		20 56	
	O Light	Turbid		0 0			O Yellow	Turbid		8 33	
5	A Yellow	Clear	8 2	42 6		32	A Yellow	Clear		54	
	B Dark	Clear	6 8	62 84			B Dark	Clear		76 8	
	O Yellow	Clear	6 4	49 72			O Yellow	Turbid		50 8	
6	A Yellow	Clear	3 8	0 89	9 23	33	A Yellow	Clear		91 40	
	B Amber	Clear	6 4	53 32	18 91		B Dark	Clear		103 32	
	O Yellow	Turbid	1 4	0 0	2 28		O Yellow	Turbid		97 12	
7	A Yellow	Clear	6 6	38 4	38 20	34	A Yellow	Clear		48 32	
	B Black	Clear	4 4	10 46	53 46		B Black	Clear		109 08	
	O Yellow	Sl turbid	3 6	0 0	49 72		O Yellow	Turbid		28 20	
8	A Yellow	Clear		80 5		35	A Yellow	Sl turbid	5 8	16 66	35 28
	B Dark	Clear		83 62			B Dark	Sl turbid	5 6	14 28	35 28
	C Yellow	Turbid		90 26			O Yellow	Sl turbid	4 8	22 22	27 77
8'	A Yellow	Clear	8 8	68 35		36	A Yellow	Clear	4 4	1 04	
	B Dark	Clear	6 9	108 61			B None				
	O Yellow	Turbid	1 8	1 36			C Yellow	Turbid	2 2	0 0	
9	A Yellow	Clear	6 8	61 52		37	A Yellow	Clear	5 4	1 35	15 11
	B Dark	Clear	7 0	88 38			B Black	Clear	4 4	1 85	8 78
	O Amber	Clear	6 4	20			C Yellow	Turbid	1 2	0 0	1 52
10	A Yellow	Clear		4 32		38	A Yellow	Clear	8 0	7 6	17 08
	B Amber	Clear		66 28			B Black	Clear	5 8	8 4	21 17
	O Yellow	Clear		75 2			O Yellow	Clear	8 6	3 2	20 82
11	A Yellow	Clear		80 3		39	A Yellow	Clear	8 4	50 6	25 54
	B Black	Clear		104 02			B Dark	Clear	5 6	100 43	28 62
	O Yellow	Turbid		42 2			O Yellow	Turbid	2 8	10 16	30 62
12	A Yellow	Clear		3 85		40	A Yellow	Clear	4 6	40 32	43 35
	B Dark	Clear		55 16			B Dark	Clear	6 7	50 25	11 00
	O Yellow	Turbid		4 18			O Yellow	Turbid	1 3	13 14	Spilled
13	A Watery	Clear	1 6	0 0		41	A Yellow	Clear	7 0	4 28	14 47
	B 0						B None				
	O Wat green	Clear	1 6	0 0			C Yellow	Turbid	1 0	1 28	6 81
14	A Yellow	Clear		28 16	16 17	42	A Yellow	Clear	5 0	50	21 86
	B Amber	Clear		26 64	8 05		B Black	Clear	4 4	54 52	25 86
	C Yellow	Turbid		5 32	11 04		O Yellow	Clear	4 6	12 06	27 62
15	A Yellow	Sl turbid	3 1	15 65	43 32	43	A Yellow	Clear	4 6	24 64	11 30
	B Dark	Clear	4 4	142 82	60 98		B Dark	Clear	4 6	46 26	16 52
	C Yellow	Turbid	1 8	16	39 42		O Yellow	Turbid	1 3	14 16	10 26
16	B Black	Clear	5 4	29 43	23 84	44	A Yellow	Clear	5 4	21 72	
	O Light	Turbid	1 8	2 16	18 26		B Black	Clear	5 8	33 21	
	D Amber	Clear	8 2	32 15	17 15		C Yellow	Sl turbid	4 6	0 0	
17	A Yellow	Clear	4 0	0 0	0 0	44'	A Yellow	Clear	5 4	33 33	
	B Amber	Clear	4 0	6 66	3 01		B Yellow	Turbid	2		
	C Yellow	Turbid	1 2	0 0	0 0		C Yellow	Clear	5 0		
18	A Yellow	Turbid	2 4	8 3	1 85	45	A Yellow	Clear		28 37	
	B Amber	Clear	4 2	55 32	8 27		B None				
	O Yellow	Turbid	1 2	0 0	0 0		C White	Water	Acid	Not done	
19	A Yellow	Clear	7 2	25 4	18 88	46	A Yellow	Clear	5 8	11 10	12 26
	B Amber	Clear	4 2	80 0	18 83		B None				
	C Yellow	Turbid	2 2	6 14	16 87		O Yellow	Turbid	2 8	1 2	6 14
20	A Amber	Clear	4 2	2 46	2 46	46'	A Yellow	Clear	6 4	13 13	6 03
	B Dark	Clear	3 8	2 19	2 19		B Dark	Clear	6 2	16 93	2 93
	O Yellow	Turbid	1 8	0 0	0 0		O Yellow	Turbid	7 8	12 29	12 29
21	A Yellow	Clear		24 24		47	A Yellow	Clear	6 0	66 64	11 30
	B Dark	Clear		38 21			B Amber	Clear	5 8	50	Toohight
	O Yellow	Turbid		2 36			C Yellow	Sl turbid	3 8	25	2 70
22	A Yellow	Clear	8 4	44 22		48	A Yellow	Clear	4 6	15 22	
	B Dark	Clear	6 8	66 16			B Black	Clear	6 2	18 88	
	C Amber	Clear	8 2	56			C Yellow	Clear	5 3	13 62	
23	A Yellow	Clear	4 8	68 66		49	A Yellow	Clear	Not done	40 00	
	B Dark	Clear	4 2	58 5			B Black	Clear	4 7	53 32	
	O Yellow	Sl turbid	3 6	5 10			O Yellow	Turbid	1 9	12	
24	A Watery	Emulsified		0 0		50	A Yellow	Clear	6 0	96 00	
	B Watery	Emulsified		0 0			B Black	Clear	6 2	32 00	
	C Watery	Emulsified		0 0			C Yellow	Clear	5 6	28 56	
25	A Yellow	Clear		6 36							
	B Dark	Clear		52 34							
	C Yellow	Turbid		2 04							

Contrary to the observations of Friedenwald,<sup>4</sup> Einhorn,<sup>5</sup> Piersol and Bockus,<sup>6</sup> in the large majority of the cases, the greatest concentration of diastase was in the darkest or second portion of the bile secretion. Of forty-seven cases in which diastase was found, thirty-one contained the highest activity in B bile, eleven in A and five in C. McClure and his associates<sup>7,10</sup> found it in B.

Trypsin plays a more divided rate, out of twenty-four estimations, ten were highest in A, nine in B, and five in C. Table 1 shows the comparisons with diastase.

When distilled water was used instead of buffer, readings in one set of tubes that did not descend in what one would take to be the normal manner were frequently obtained. Tube 3 in each of the sets often would show a low reading in contrast to the one above and to that below.

TABLE 2—Results of the Activity of the Enzyme in a Dilution of 1:600

Amount of 1:600 Dilution	Amount of Glucose in 100 Cc	Factor	Cor- rected Results	Amount of 1:600 Dilution	Amount of Glucose in 100 Cc	Factor	Cor- rected Results
A 1.0 cc ==	29.43 mg	× 1	== 29.43	C 1.0 cc ==	71.42 mg	× 1	== 71.42
0.8 cc ==	19.22 mg	× 1.25	== 24.125	0.8 cc ==	50.00 mg	× 1.25	== 62.5
0.6 cc ==	16.66 mg	× 1.66	== 26.55	0.6 cc ==	38.84 mg	× 1.66	== 62.5
0.4 cc ==	11.32 mg	× 2.5	== 28.3	0.4 cc ==	18.06 mg	× 2.5	== 45.2
0.2 cc ==	4.15 mg	× 5	== 20.75	0.2 cc ==	7.48 mg	× 5	== 37.4
B 1.0 cc ==	38.40 mg	× 1	== 38.70	D 1.0 cc ==	62.28 mg	× 1	== 62.28
0.8 cc ==	30.76 mg	× 1.25	== 38.32	0.8 cc ==	44.44 mg	× 1.25	== 55.54
0.6 cc ==	26.42 mg	× 1.66	== 43.66	0.6 cc ==	30.76 mg	× 1.66	== 51.26
0.4 cc ==	18.37 mg	× 2.5	== 45.92	0.4 cc ==	16.33 mg	× 2.5	== 40.8
0.2 cc ==	8.46 mg	× 5	== 42.30	0.2 cc ==	5.55 mg	× 5	== 27.75

At times there was no reduction. This happened frequently, and as yet there is no explanation to offer. When the buffer solutions were used, this straightened itself out, and a more or less regular steplike descent was obtained. Some typical results in the activity of the enzyme in a dilution of 1:600 are shown in table 2.

4 Friedenwald and Sindler. Fractional Analysis of Duodenal Contents in Normal Individuals, J. A. M. A. **77** 1469 (Nov. 5) 1921.

5 Einhorn. M. Rec. June 15, 1920, vol. 99, The Duodenal Tube, Philadelphia, W. B. Saunders Co., 1921.

6 Piersol, G. M., and Bockus, H. L. Pancreatic Enzymes in Cholecystitis, Arch. Int. Med. **35** 204 (Feb.) 1925.

7 McClure, C. W., Wetmore, A. S., and Reynolds, Lawrence. New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, Arch. Int. Med. **27** 706 (June) 1921.

8 McClure, C. W., and Wetmore, A. S. Enzyme Concentration of Duodenal Contents After Ingestion of Pure Food Stuffs and Food Mixtures by Normal Man, Boston M. & S. J. **187** 882 (Dec. 14) 1922.

9 McClure, C. W., and Jones, C. M. Enzyme Concentration of Duodenal Contents in Pathological Conditions Involving Pancreas, Liver and Stomach, Boston M. & S. J. **187** 909 (Dec.) 1922.

10 McClure, C. W., Montague, O. C., and Campbell, L. L. Studies on the Mechanism of External Pancreatic Secretion, Boston M. & S. J. **192** 527 (March 19) 1925.

The multiplication that is carried out in each of the series is the figure required to bring the fraction of a cubic centimeter of enzyme back to its unity—1. A glance at the results reveals two divergent phenomena. In *C* and *D*, there is a constant descent in the activity of the enzyme. In other words, as the duodenal contents become more diluted, the enzyme loses strength faster than can be accounted for by the adding of buffer solution. Results of this type occurred in about 50 per cent of the cases. In 25 per cent a gradual increase was seen as in *B*, at times dropping off considerably in the last tube as in *A*. This is more likely to be the case when tube 5 gives but a slight reduction. With this in mind it is felt that the highest dilution that can be used safely is the one which was adopted as the standard, 1/600.

The estimation of trypsin is at best but a whimsical thing. It seems to vary at times in fair accord with the diastase, at other times it appears to run on a path of its own. In many cases, especially when the diastase is low, the pepsin appears to play a big rôle in the digestion of casein.

From clear gastric juice obtained from fasting stomachs, from stomachs showing no biliary regurgitation, as high nonprotein nitrogen readings were obtained from casein digestion as in the usual run of trypsin tests. I believe, however, that when both the diastase and trypsin are low, one may be assured that the case is one of deficient pancreatic secretion. This estimation acts more in the manner of a double check or a method for making assurance doubly sure than in any positive manner. I never obtained a low trypsin reading without simultaneously finding a similar diminution in diastase. Trypsin estimations were secured in only two cases of achylia, in both instances normal enzymic activities were found. In neither of these cases was the pepsin index of the gastric contents estimated. This should have been done and will be done at the first available opportunity.

I have never seen any work that would be thoroughly convincing of the individual variation of the enzymes. From the work of Mellanby,<sup>11</sup> Anrep, Lush and Palmer<sup>12</sup> and others, I believe that the enzymes are secreted in the same manner irrespective of the stimulation that they have received. D. H. Dolley<sup>13</sup> can find no basis for the unequal secretion of the enzymes. No objective differences that would account for the variation in function are apparent in the histology of the gland. Histologically, all cells are similar and go through the same stage of metabolic rest and activity.

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11 Mellanby, J. The Mechanism of Pancreatic Digestion, the Function of Secretion, *J. Physiol.* **60** 85 (May) 1925.

12 Anrep, G. V., Lush, J. L., and Palmer, M. G. Observations on Pancreatic Secretion, *J. Physiol.* **59** 434 (March) 1925.

13 D. H. Dolley. The General Morphology of Pancreatic Cell Function in Terms of Nucleocytoplasmic Relation, *Am. J. Anat.* **35** 153 (May) 1925.

As shown in a previous paper, there is usually a difference in the hydrogen ion concentration of the various portions. Practically all of them are on the acid side, although in a few cases, two cases of achylia plus six others, one or two readings are on the alkaline side. The low  $p_H$  in the last fraction, therefore, can be nothing else than hydrochloric acid which has come through in increasing amounts as the drainage has progressed. The low hydrogen ion concentration usually found in the last part of the drainage cannot be connected with the weak enzymic activity so frequently found in the C bile. Specimens in which the reduction has been marked have been noted, and just as frequently with a low as with a high hydrogen ion concentration. One with a reduction of 100 mg in an acid portion is one of the highest enzymic concentrations in the entire series. A lowering of enzymic activity in C with a high  $p_H$ , however, has never been noted. This lowering is taken to be more of a dilution phenomenon than any real stoppage of secretion caused by the increasing acidity.

In a small series a saliva control was run in connection with the usual three series of tubes, but any connection between the amount of diastase digestion and that seen in ptyalin was not found. Some of the estimations at  $p_H$  5.6-5.8, one at which ptyalin is considerably embarrassed, were run through and lowered, but good reductions from the pancreatic enzymes were secured. The returns from gastric secretions taken just before the tube had entered the duodenum also showed no ptyalin activity. These observations have led my co-workers and me to adopt the following method—a method for the estimation of diastase which, it is felt, gives a fairly correct idea of the pancreatic function in the production of enzymes.

#### METHOD

It has been shown in the foregoing that the enzyme concentration of that part of the duodenal contents contained in the darkest biliary secretion, commonly known as B bile, is usually the most active of all portions. When it is not, its activity is such that it can be taken to represent the functional activity of the pancreas. When this portion is turbid, due to precipitation of the bile pigments by hydrochloric acid, the use of clear A bile is suggested.

After thorough centrifugalization, 1 cc of this is placed in 19 cc of buffer solution  $p_H$  7.7 and 1 cc of the 1/20 mixture in 29 cc of the same buffer. This makes a 1/600 dilution. These two dilutions are sufficient.

Into three Folin and Wu blood sugar tubes are placed respectively, 1 cc of the 1/20 dilution measured from an accurate 1 cc pipet, 0.1 cc from a 0.1 cc pipet, of the 1/20 dilution with 0.9 cc standard buffer, 1 cc of the 1/600 dilution. To each tube is added 1 cc of 1 per cent starch solution made up by boiling as directed. This is incubated for thirty minutes in a water bath, 38 to 40 C, and 2 cc alkaline copper sulphate of Folin and Wu added and carried out as directed by them for blood sugar determination. In normal cases the digestion in tubes 1 and 2 will be practically complete, certainly in 1. Tube 3 will be the only one necessary to read. If this reduction is low, it will be safe to take the 1/200 tube as representing the true pancreatic activity. This has been found to

be the case as shown in the foregoing determinations in a series of five tubes with progressively smaller amount of each biliary fraction in 1 600 dilution have been conducted The milligrams of dextrose produced from one cc of starch are then calculated

To arrive at a unit of comparison this simply necessitated the multiplication of the amount found in tube 3 by 100, in tube 2 by 33.3 and in tube 1 with a dilution of 1 20 by 3.3 For instance, in tube 3 the colorimetric reading of  $\frac{\text{Standard}}{\text{Unknown}} \times \text{amount of glucose in standard} \times 100 = \text{mg of glucose}$ , or to give an example using standard 2 of glucose working standard,  $\frac{20}{15} \times 0.4 \text{ mg} \times 100 = \text{mg}$  This represents 100 times the amount of glucose produced from one cc — 1 per cent starch — by the action of 1 600 dilution of pancreatic enzyme as obtained by duodenal drainage

TABLE 3—Diseases Diagnosed and Enzyme Concentrations

Chronic Infections	Gall stones	Chronic Biliary Infection	Psychoneurosis	Spastic Colitis	Banti's Disease	Carcinoma Stomach	Visceroptosis	Migraine	Diabetes	Carcinomatous Pancreas	Chronic Appendicitis	Angioretic Edema
1.85	66	50	54	53	11.1	71	28	4.2	142	0.0	76	1.4
8.4	38	66	46		10.11		55	66.0				
32.0	75	30	33-33		6.05							
	104	28	96									
	38	22	103									
	100	62	62									
	57	53										
	17-11	103-83										
	0.0	6										
		53										
		80										
		2.4										
		52										
		71										
		12										
		109										
		88										

MATERIAL

Of the fifty people examined, ten of them were considered normal, that is, they had no symptoms which could be associated with biliary or with pancreatic disease Six of them, as far as was known, were psychoneurotic persons They were examined for the express purpose of obtaining controls, one other had what was taken to be chronic appendicitis, one, spastic colitis and the last two, visceroptosis Except in one instance, the highest readings were obtained in the B portions, that one was obtained in an A portion The readings averaged between 28 and 103, six of them were between 30 and 70 After thorough study of the figures it was felt that readings between these limits can be called the average Figures below that are suggestive of a decreased function, and those above are considered only as secretion in which the percentage of enzyme to pancreatic fluid is high As yet it has been impossible to attach any significance to it, comparable, for instance, to hyperchlorhydria

Table 3 shows the diseases diagnosed in the various patients with the various enzyme concentrations given below The great majority were the private patients of Dr Thomas A Brown, and the diagnoses were made by him The others were made by Dr E H Gaither and by me The diagnoses were made by the usual clinical and laboratory methods without consideration of the results obtained by duodenal drainage

Fifty per cent of the patients examined had diseased biliary tracts. Most of the observations noted here I have discussed in article on biliary drainage in which I endeavored to correlate the mass of observations. It is interesting that in 20 per cent of the observations a distinct lowering of pancreatic enzyme activity was discovered. Two of the patients had chronic infectious arthritis, one had angioneurotic edema and one had migraine.

TABLE 4—*Columns of Low, Medium and High Enzyme Activity Showing Admixture of Diseases*

84 Arthritis	30 Chronic biliary disease	80 Chronic biliary disease
18 Arthritis	32 Arthritis	83 Gallstones
00 Carcinoma pancreatic head	38 Gallstones	88 Chronic biliary disease
60 Chronic biliary disease	38 Gallstones	96 Psychoneurosis
24 Chronic biliary disease	33 Psychoneurosis	100 Gallstones
42 Migraine	46 Psychoneurosis	104 Gallstones, jaundice
00 Cholelithiasis	57 Gallstones	100 Gallstones
14 Angioneurotic edema	50 Chronic biliary disease	108 Gallstones
	53 Chronic biliary disease	103 Psychoneurosis
	55 Chronic biliary disease	142 Diabetes
	53 Colitis	102 Gallstones
	52 Chronic biliary disease	
17} Gallstones	54 Chronic biliary disease	
11} Gallstones	66 Gallstones	
12 Chronic biliary disease	62 Chronic biliary disease	
11} Gallstones	66 Chronic biliary disease	
10} Banti's disease	66 Migraine	
6} Gallstones	62 Psychoneurosis	
22 Chronic biliary disease	71 Chronic biliary disease	
28 Visceroperitonitis	75 Gallstones	
28 Chronic biliary disease	76 Chronic Appendicitis	

#### COMMENT

While a pancreatic stimulant was being sought, the different food portions used by McClure, Wetmore and Reynolds,<sup>7</sup> Bassler<sup>14</sup> and Lyon<sup>15</sup> were considered, the use of magnesium sulphate was decided on for these reasons:

1 It leaves the field of work rapidly after injection, and it is unnecessary to contend with more dilution since this is already produced by the biliary, gastric and duodenal secretions.

2 Certain people are notoriously affected by different types of food, and a great many of them experience unpleasant symptoms after the use of fat.

3 I believe that more definite results can be obtained if magnesium sulphate is used as the standard stimulant, and I cannot agree with

<sup>14</sup> Bassler Quantitative Tests of Digestive Pancreatic Activity Easily Applied Clinically, Arch Int Med **35** 162 (Feb) 1925

<sup>15</sup> Lyon, Vincent Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts, J A M A **73** 980 (Sept 27) 1919, The Treatment of Catarrhal Jaundice by Rational, Direct and Effective Method, Am J M Sc **159** 503 (April) 1920

Dr Bassler that "By employing the food stimulant we obtain the storage factor of the gland, and as a pancreas is deficient in this, it is deficient in its running secretory function. The storage factor of all gland cells during rest is the best index of the organ function, and of its activity during the complete range of active secretion." The activity of the enzymes can be measured, but it is impossible as yet to measure the entire quantitative output of the gland or its storage ability. At present in cases of low readings it cannot be said whether there is a diminution in the strength of the enzyme as might come about by unfavorable changes in  $p_H$  or temperature or whether the percentage of enzyme in the pancreatic juice is low. This of course involves the dual stimulation of the organ by secretin and by the vagus. Mellanby and Aurep, Lush and Palmer have shown that in a pancreas in which secretion has been exhausted stimulation of the vagus will produce a restoration of the digestive juices equal to that estimated in the first flow.

My co-workers and I have frequently kept a 1:20 dilution over night and repeated the estimation in tube 1 of each series the next day, with practically no change in the activity of the enzyme. As was suggested by Dr Brown,<sup>1</sup> and further brought out by Dr McClure<sup>16</sup> and his co-workers, it is found that free hydrochloric acid is not needed to stimulate the flow of pancreatic juice. Dr Brown was estimating diastase in the stools and found normal amounts in cases of achylia. The Boston writers also found this by duodenal drainage. Recently Mellanby and Huggett<sup>17</sup> concluded from a careful series of experiments that "There is no evidence that gastric hydrochloric acid converts a precursor (prosecretin) in the duodenal mucosa into secretin and thereby elicits a flow of pancreatic juice. The results show that the secretin mechanism for the production of pancreatic juice may function in complete gastric achlorahydria."

In two cases of achylia I saw a high activity in one and a definite but lower activity in the other. In two normal patients it was possible to stimulate a normal flow of pancreatic enzymes by the injection, through the duodenal tube, of 5 cc of filtered achylic fluid recovered that same morning from the stomach contents of patients with chronic gallbladder disease. These readings were similar in amount to those attained later in the same patient when stimulated by magnesium sulphate. In neither of these persons did the initial stimulus provoke a flow of *B* bile.

16 McClure, Montague, and Mortimer. Pancreatic Function in the Absence of Free Hydrochloric Acid from the Stomach, Boston M & S J **190** 357 (Feb 28) 1924

17 Mellanby and Huggett. The Relation of Secretion Formation to the Entrance of Acid Chyme into the Small Intestines, the Properties of Secretion, J Physiol **61** 122 (March) 1926

Pierson and Bockus,<sup>4</sup> when using Metts' method as modified by Einhorn,<sup>5</sup> which consists in placing tubes of agar, containing starch, hemoglobin or olive oil into the return from the duodenal tube, found the highest enzyme activity in the first portion unstimulated. They also add, "The most disappointing part of the normal group is the wide fluctuation which occurs in the same patient when the pancreatic function is tested more than once under exactly the same conditions." This apparent divergence in observations probably lies in the fact that in using the pure duodenal juice they were not controlling their hydrogen ion concentration, and this can easily vary from day to day according to the tone and secretion of the stomach. A low  $p_H$  will, of course, give lowered digestion. Their finding of the greatest digestion in the first flow is probably due to the fact that this was the portion having the highest  $p_H$ . Two or more examinations have been made on several patients at different times, and it can safely be said that the results are comparable.

I have found that apparently there is some direct connection between the stimulation for a flow of bile and pancreatic secretions, and I have never been able to isolate the pancreatic from the biliary flow. This feature in itself offers one of the best diagnostic factors. The differentiation of stone in the common duct and carcinoma can be made relatively easily by the absence of bile flow and by the appearance of pancreatic juice. At times, however, it is possible to get a stoppage of flow from both organs by a stone blocking the ampulla of Vater so as to shut off the entire flow. This, according to Lund,<sup>18</sup> also Mann and Giordano,<sup>19</sup> is rarely possible because of the anatomy of the junction. A pancreatitis may be combined with the stone and prevent secretion. The appearance of only microscopic elements of bile makes one dubious about a diagnosis of carcinoma of the head of the pancreas.

In the eleven patients who have definite low pancreatic readings, all but two have definite clinical signs of hepatic pathologic changes. These patients had arthritis. Those with migraine and angioneurotic edema have improved considerably since they have been placed on treatment instituted to assist their hyperemic livers. Just why two of three patients with arthritis should have this condition I do not know. On the other hand, there are seventeen patients who have chronic biliary disease and eight who have gallstones, a group of twenty-five, of which five, or 20 per cent, have a marked functional pancreatic defect.

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18 White, F. W. The Value of Medical Biliary Drainage for Diagnosis and Treatment of Disease of the Gallbladder and Bile Ducts, Boston M. & S. J. 186 206 (Feb. 16) 1922.

19 Mann and Giordano. The Bile Factor in Pancreatitis, Arch. Surg. 6 1 (Jan.) 1923.

A great deal is written today concerning the involvement of the pancreas subsequent to infection of the biliary tract. Joslin<sup>20</sup> feels that this is the starting point in many cases of diabetes, and that cholelithiasis is a danger signal. Chester M. Jones<sup>21</sup> agrees with him and adds that all cases of cholelithiasis require surgical intervention. Moynihan<sup>22</sup> feels that "chronic pancreatitis is generally caused by gallstone irritation," Judd,<sup>23</sup> in reviewing a large series of cases, shows that "pancreatitis occurs frequently with cholecystitis and as a result a definite gross change occurs in the pancreas. It is possible for infection to involve the pancreas by way of the lymphatics from the gallbladder, and in many cases this probably explains the source of the infection. It is apparently entirely removed by the treatment for cholecystitis." Piersol and Bockus,<sup>6</sup> after studying forty cases of cholecystitis by the method described in the foregoing, find a reduction in the amount of pancreatic enzyme in 85 per cent of the cases.

In consideration of my observations, I do not feel that one is justified in being too pronounced in one's views on the occurrence of pancreatitis with biliary tract infection. Certainly a large percentage of the cases, most of which were diagnosed by a skilled physician, show a normal, and some of the gallstone cases a strikingly high, pancreatic secretion. The present series of cases is of course too small to enable one to draw any satisfactory conclusions.

Administration of pancreatic extract, which has been demonstrated by Aaron, Wadsworth and Schneider<sup>24</sup> to reach the duodenum and to be effective, may be of some value in these cases of lowered pancreatic activity.

#### CONCLUSIONS

I feel that a relatively simple and accurate method for the estimation of pancreatic enzyme activity is here offered. This method can easily be followed in any small laboratory. The amount of equipment needed is small, and the time consumed not much longer than that needed in making blood chemistry studies.

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20 Joslin. *Treatment of Diabetes Mellitus*, ed 3, Philadelphia, Lea & Febiger, 1923, p 479.

21 Jones, C. M., Castle, W. B., Milholland, H. B., and Bailey, Francis. *Pancreatic and Hepatic Activity in Diabetes Mellitus*, *Arch Int Med* **35** 315 (March) 1925.

22 Moynihan. *Abdominal Operations*, Philadelphia, W. B. Saunders Company, 1916.

23 Judd. *Collected Papers of Mayo Clinics, Relation of Liver and Pancreas to Infection of Gallbladder*, 1921.

24 Aaron, A. H., Wadsworth, J. V., and Schneider, H. C. *The Enzymic Activity of the Duodenal Contents Following the Ingestion of Pancreatin*, *Arch Int Med* **37** 408 (March) 1926.

It is of paramount help in making a differential diagnosis in cholelithiasis and in cancer of the head of the pancreas

It is possible that it may serve as a diagnostic method in the determination of the chronic pancreatitis that occurs with many conditions and which may be helped by pancreatic extracts

If a low pancreatic activity is discovered which is associated with gallstones or with a chronic biliary infection, and which does not improve following the institution of treatment for the hepatic condition, one should think seriously of a cholecystectomy

# BILIARY, PANCREATIC AND DUODENAL STUDIES

## III ESTIMATION OF VALUE OF DUODENAL DRAINAGE FOR THE DIAGNOSIS OF BILIARY DISEASE BASED ON THE EXAMINATION OF FIFTY PATIENTS

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I shall first give a brief sketch of the progress of opinion on the function of the gallbladder

In 1893, Doyon<sup>1</sup> carried out experiments on the gallbladder of dogs in situ in a manner which convinced him that there were definite contractions of the organ, and that these contractions were increased by stimulation of the sympathetic nerves. Later Courtade and Guyon<sup>2</sup> demonstrated that the vagus also contained motor fibers to this organ. In 1905, Bainbridge and Dale,<sup>3</sup> two of England's foremost physiologists, published some conclusive observations, "The gallbladder shows rhythmic variations in volume. The rhythm is increased in extent after the removal of tonic inhibitory impulses. The normal effect of stimulation of the sympathetic nerve supply to the muscular coat of the gallbladder, whether by electrical excitation of the right splanchnic or by intravenous injection of adrenalin, is relaxation. The apparently motor effects first described by Doyon are in all probability due to extraneous causes, namely, the mechanical pressure on the gallbladder caused by swelling of the liver and the increased tone of the muscle due to hyperemia." The observations of Courtade and Guyon that the vagus contains motor fibers for the gallbladder have been confirmed.

Courtade and Guyon were unable to elicit reflex contractions of the gallbladder by applying acid or the products of gastric digestion to the duodenal mucous membrane or to the biliary papilli. They also found an admixture of motor fibers in the right splanchnic nerve, "the presence of which can be detected when the tone of the gallbladder is lowered by enfeeblement or stoppage of the circulation." These observations were later confirmed by Lieb and McWharter<sup>4</sup> in 1915. Freese<sup>5</sup> found

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1 Doyon. Contribution a l'etude de la contractilite de voie biliaire, Arch de physiol norm et path **25** 673, 1893

2 Courtade and Guyon. Action motrice du pneumogastrique sur la vesicule biliaire, Compt rend Soc de biol, 1904, pp 313, Trajet des nerfs extrinseque, De la vesicule biliaire, 1904, p 874

3 Bainbridge and Dale. The Contractile Mechanism of the Gallbladder and Its Extrinsic Nervous Control, J Physiol **33** 138, 1905-1906

4 Lieb and McWharter. Action of Drugs on the Isolated Gallbladder, J Pharmacol & Exper Ther **7** 83, 1915

5 Freese, J. H. The Force of Contraction of the Gallbladder and the Origin of Its Motor and Inhibitory Nerve Fibres, Bull Johns Hopkins Hosp **16** 235, 1905

motor and inhibitory fibers in the splanchnic nerves. He also found that the gallbladder contracted, but that its maximum force "does not exceed materially the maximum secretion pressure of the bile." Seizaburo Okado,<sup>6</sup> on the other hand, concludes that the rhythmic contractions of the gallbladder are strong enough to expel bile into the duodenum, because after stimulation of this intestinal segment with acids and products of food digestion, he noted spurts of bile coming through the ampulla of Vater. He concluded that these materials were reflexly stimulating the gallbladder. These observations, however, are not proof that the gallbladder does contract enough under such stimuli to empty itself.

The work of Auster and Crohn<sup>7</sup> and that of Diamond<sup>8</sup> is also enlightening on this point. After injection of methylene blue in the gallbladder, Auster and Crohn were unable to produce an expulsion of the contents. Dr. Diamond injected a carmine suspension and was able to collect all the bile through a closed duodenal fistula, only at rare intervals could he detect any of the carmine in the bile, and at the end of six weeks he was able to find practically all of it still in the gallbladder. "When the bile was entirely replaced by carmine, one found but very little bile in the neck of the gland at the end of a week."

In the light of the great volume of work done by Peyton Rous, McMaster and Broun,<sup>9</sup> who were able to watch the filling of the previously emptied gallbladder by one half or one third of the bile flow while they collected the rest directly from the hepatic ducts of dogs, the foreign body reaction of carmine undoubtedly has a great deal to do with shutting out the inflow of bile. This bile, the Rockefeller writers<sup>10</sup> show, becomes greatly concentrated, the pigment content becoming eight to ten times that of the hepatic bile. It is possible that the entire amount would be absorbed, but it does seem more likely that there should be a gradual depletion of the reservoir to make room for more. Rost,<sup>11</sup> also Klee and Kupfel<sup>12</sup> in repeating Post's work, making a closed duodenal fistula with a window so that they could watch the ampulla of

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6 Okado, S. On the Contractile Movements of the Gallbladder, *J. Physiol* **49** 457, 1915, **50** 42 1915-1916

7 Auster, L. S., and Crohn, B. B. Notes on Studies in the Physiology of the Gallbladder, *Am. J. M. Sc.* **164** 345 (Sept.) 1922

8 Diamond, J. S. An Experimental Study of the Meltzer-Lyon Test with Comment on the Physiology of the Gallbladder and Sphincter Vateri, *Am. J. M. Sc.* **166** 894 (Dec.) 1923

9 Rous, P., and McMaster, P. D. A Method for Permanent Sterile Drainage of Intraabdominal Ducts as Applied to Common Duct, *J. Exper. Med.* **37** 11 (Jan.) 1923

10 Rous, P., and McMaster, P. D. The Concentrating Activity of the Gallbladder, *J. Exper. Med.* **34** 47 (July) 1921, *Proc. Soc. Exper. Biol. & Med.* **22** 215, 1920

11 Rost, F. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **26** 770, 1913

12 Klee and Kupfel. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **27** 789, 1914

Vater, found slight secretion during periods of fasting, after stimulation with peptone or a meal, however, they saw gushes of dark heavy bile that they took to be that from the gallbladder

The article of Meltzer<sup>13</sup> in which he applies, "the law of contrary innervation" to the relation between the gallbladder and sphincter of Oddi in the same manner that it is applied to the detrusor muscle and to the urinary bladder sphincter, attracted the attention of Dr B B Vincent Lyon<sup>14</sup> of Philadelphia. Struck by the possibility of the results to be obtained by the application of Meltzer's now famous footnote, he started to make a series of duodenal drainages. In a preliminary article he quotes the footnote and adds, "This simple footnote served as an inspiration for a clinical experimental study on human beings, at first with magnesium sulphate and later with other solutions. I believe that the experimental observations on animals as conducted by Meltzer have borne fruit and have opened up a new method of diagnosing diseases of the gallbladder and biliary tract." In much the same way this preliminary article of Lyon's, brought out in all seriousness and honesty, with firm belief in its accuracy, has turned a storm of attention and investigation to the liver and things biliary. In its turn it has brought forth a torrent of literature much too great to be amusing, much too exploitable for the charlatan to miss and much too inaccurate to be worthy of scientific consideration. Many competent men have studied the process, such men as Alvarez,<sup>15</sup> Einhorn,<sup>16</sup> and Cutler,<sup>17</sup> drop it as fruitless or to add some such remark as that of Alvarez, "I agree with Lyon that it is worth trying in many cases in which surgical help must be postponed or refused." On the other hand, there are such men as Smithies,<sup>18</sup> Oleson,<sup>19</sup> Franklin White,<sup>20</sup> Crohn, Reiss and

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13 Meltzer, J S. The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Disease of the Bile Ducts and the Gallbladder, *Am J M Sc* **153** 469, 1917

14 Lyon, V B B. Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts, *J A M A* **73** 980 (Sept 27) 1919

15 Alvarez, W C. Diagnosis and Treatment of Gallbladder Disease with Especial Reference to the Meltzer-Lyons Test, *M Clin N Amer* **6** 213 (Sept) 1922

16 Einhorn, M. Action of Various Salts and Other Substances on the Liver After Introduction Into the Duodenum, *New York M J* **113** 313 (Feb) 1921

17 Cutler, E C, and Newton, F C. Some Experiences with the Meltzer-Lyon Test in Gallbladder Disease, *Surg Gynec Obst* **35** 146 (Aug) 1922

18 Smithies, Frank. Non-Surgical Drainage of the Biliary Tract, Its Usefulness as a Diagnostic and Therapeutic Agent, *Illinois M J* **39** 325 (April) 1921

19 Smithies, F, and Oleson, R B. The Diagnostic and Therapeutic Value of Non-Surgical Biliary Tract Drainage in Patients Exhibiting Biliary Tract Disease Upon Whom Surgical Procedures Have Been Performed Previously, *Illinois M J* **41** 29 (Jan) 1922

20 White, F W. The Value of Medical Biliary for Diagnosis and Treatment of Disease of the Gallbladder and Bile Ducts, *Boston M & S J* **186** 206 (Feb) 1922

Radin,<sup>21</sup> who believe in it both from a diagnostic and from a therapeutic point of view Chester M. Jones<sup>22</sup> of Boston, who recently wrote a well rounded article on the subject, thinks it has its possibilities in both directions

#### EXPERIMENTAL WORK

My co-workers and I have recently performed duodenal drainage in a fairly large number of cases, the last fifty of which are reported here, for we feel that in them our method of investigation has become more complete. Our method of getting the tube in place, which is essentially that described by Lyon, has been described in detail in a previous article on the estimation of pancreatic enzymes<sup>23</sup>

- 1 The tube is swallowed by the patient who has been fasting for twelve hours
- 2 With the tube in his stomach the patient assumes a right lateral position, and by siphonage the contents are collected into a beaker
- 3 The patient is not allowed to swallow saliva
- 4 The tube is allowed to drift into the duodenum, and its position is determined with the use of a fluoroscope
- 5 With the tube in the bend of the duodenum, a secretion of pancreas and bile is stimulated with warm magnesium sulphate. This is injected slowly through the tube

After stimulation with magnesium sulphate, 40 cc of a 33 per cent solution, we divided the different colored portions obtained into separate containers, collecting adequate portions of each lot in sterile centrifuge tubes. This was done for the bacteriologic studies

Frequently our first knowledge of the presence of the tube in the duodenum was a clear flow of golden clear bile, at times a light turbid yellow bile and at others a deep brown colored bile. Not infrequently one obtains a free flow of bile colored fluid before the tube is out of the stomach. This biliary regurgitation is a common observation to those in the habit of pumping out a fasting stomach. We do not see any justification of calling this a dysfunction of the sphincter of Oddi. This flow soon ceases, and after magnesium sulphate stimulation, the usual clear flow of A, of the dark clear B and of the C bile, a light less viscid fluid but much more frequently turbid than clear and transparent, is obtained. If the flow is allowed to continue, it becomes thinner in pigment and shows a greater amount of free hydrochloric acid as well as total acidity.

The hydrogen ion concentration of these various portions is enlightening. In all we have obtained the hydrogen ion concentration in about twenty-five cases, but rarely have we obtained readings higher than neutrality—twice in patients with gastric achlorhydria and five times in patients with normal gastric analysis. All of these persons showed a reading less than neutrality in some fraction. The  $p_H$  in A averages were around 4.2 to 6.8, with a range from  $p_H$  2.4 to 8.6. This last reading was not obtained in a patient with achylia, note the C bile of the same patient,  $p_H$  1.8. The  $p_H$  of B tends to be lower than that of A bile and in the patients examined never rose above neutrality. The  $p_H$  of C bile tends to be low, usually between 1.4 and 2.4, twice it was above 7, one of these patients having

21 Crohn, B. B., Reiss, J., and Radin, M. Experiences with Lyon Test for the Determination of Gallbladder Disease, *J. A. M. A.* **76** 1567 (June 4) 1921

22 Jones, C. M. Rational Use of Duodenal Drainage, *Arch. Int. Med.* **34** 60 (July) 1924

23 Martin, Lay. The Estimation of Pancreatic Enzymes and the Value of Such Determination from a Clinical Standpoint, *Arch. Int. Med.* **39** 343 (March) 1927

achylia Whenever the C bile is really turbid, it is always below  $p_H$  3 The colorimetric sets were made in exact accord with the method of Clark<sup>24</sup>

At times one sees the light turbid yellow C bile alternating with the typical dark B bile This often continues for a period of time, and to localize the area from which it was coming, at first caused us no little concern This question was solved, however, on adding varying amounts of tenth normal sodium hydroxide to the turbid tube and on having the so-called C bile change into a typical clear B bile before one's eyes, a trifle lighter, of course, than the one with which we were comparing it on account of the admixture of gastric secretion and alkali One may take a portion of the usual B bile and by the addition of proper amounts of tenth normal hydrochloric acid obtain the counterpart to the original turbid C bile This change occurs at a  $p_H$  3.4 to 3, and by raising the hydrogen ion concentration the original B bile may once more be obtained In case 15 (table 3), with no A bile we obtained a good flow of B,  $p_H$  5.4, and a turbid C bile  $p_H$  1.8, this changed to a typical B bile  $p_H$  8.4 and remained so This, of course, explains the absence of B bile in cases in which this condition is at times taken to represent a pathologic condition in the gallbladder or cystic duct

As my co-workers and I had obtained high nonprotein nitrogen estimations in the thick inspissated bile from the gallbladders of two patients with carcinoma of the head of the pancreas, we made similar determinations in the three fractions in thirty-six cases hoping that it would give us some clue concerning the origin of B bile

#### METHOD

To 5 cc of bile about one-fourth the amount of acid animal charcoal is added This is mixed thoroughly and allowed to stand for thirty minutes Five cubic centimeters of 10 per cent sodium tungstate and of two-thirds normal sulphuric acid are added The solution is mixed and allowed to stand for fifteen minutes or more Water is added to 50 cc, and allowed to stand overnight in the icebox The solution is filtered and the amount of nonprotein nitrogen is determined by the nesslerization method of Folin and Wu for blood<sup>25</sup>

Frequently the rapid addition of Nessler's solution will cause a clouding If this persists, a filtering of the fluid removes the cloudiness and does not seem to lower the reading This may be ascertained by making a second digestion Just why there is a precipitation at one time and not at another we do not know

The highest readings for the series was found twenty-four times in B, ten times in A and two times in C bile

In three cases in which no bile was obtained from the duodenal contents, one not listed here, the results shown in table 1 were obtained

TABLE 1—*Diastase and Nonprotein Nitrogen Estimations in Three Cases*

Diagnosis		Diastase	Nonprotein Nitrogen
Carcinoma of head of pancreas	{ A	0	Too light
	{ B	0	Too light
	{ C	0	Too light
Choledocholithiasis	{ A	0	13
	{ B	0	Not done
	{ C	0	25
Catarrhal jaundice	{ A		12
	{ B	29 36	
	{ C		25

The range of reading varies from too light to read to 59 mg per one hundred cubic centimeters of bile The majority of the estimations for all readings are between 15 and 35 mg per hundred cubic centimeters of bile

24 Clark, W M The Determination of the Hydrogen Ion, Baltimore, Williams & Wilkins Co, 1925

25 Stitt Practical Bacteriology, Blood Work and Animal Parasitology, ed 7, Philadelphia, P Blakiston's Son & Company, 1923

## BACTERIOLOGY

Cultures were made from each tube direct to human blood agar plates. The hydrogen ion concentration of the agar was 6.8. Cultures were taken from forty-two specimens of bile. In five of these no growth was obtained (certainly some organisms should have been obtained in three of these as they had definite gallbladder symptoms). The common organisms found were staphylococci, streptococci, hemolytic and nonhemolytic; colon bacilli, a thin gram-negative bacilli growing like influenza, gram-positive diplococci and large ovoid gram-positive cocci that I have been unable to identify. I do not think it is air borne, as I have obtained the same organisms from patients on whom drainage

TABLE 2—*Microscopic Observations on Fresh and Stained Preparations*

	Portion	Quality	p <sub>H</sub>	Fresh Preparation	Stained Preparation
Arthritis	A	None obtained			
	B	Clear, dark	5.0	Feathery residue often gathered together to resemble lymphoid cells, no pus seen	Scattered pigment, no bacteria, no cells
	C	Turbid, light	1.8*	Feathery residue +++, polymorphonuclears ++, lymphocytes +, nuclei	Many diplococci, many white blood cells and epithelial cells
Chronic biliary infection	A	Clear, golden	6.6	Few feathery flocculi	Scattered pigment
	B	Dark, clear	4.4	Scattered feathery residue, few cholesterol crystals	No cells, no pus
	C	Slightly turbid, yellow	3.6	Slight feathery residue, some scattered clumps of white blood cells	Streptobacilli and white blood cells
Chronic biliary infection with stones	A	Clear	8.0	Practically nothing	0
	B	Clear, very dark, 110 cc	5.2	Slight feathery residue	Scattered pigment and few bacilli
	C	Clear, light	8.4	Crystals looking like fat globules	0

\* When C bile is acidified below p<sub>H</sub> 3.2, the bile pigment (feathery residue) precipitates out in great abundance.

has been performed in different locations and from whom cultures were taken immediately. Usually more than one organism is obtained, frequently three.

In stained smears there are often large clumps of bacteria, usually in C bile. In a few cases they were exceedingly numerous in B bile, but the records show that this occurs with patients whose p<sub>H</sub> is rather low. In one case the bacteria were surrounded by clumps of pigment, the whole field giving the appearance of round cell infiltration about a focus.

*Sediment*—In the turbid C bile in the series a large mass of feathery residue was always found at the bottom of the tube. The amount found in A and B bile seems to bear a direct relation to the hydrogen ion concentration, the higher the p<sub>H</sub> the less the amount of sediment.

TABLE 3—Results Obtained from the Examination of Fifty Patients

	Color	Quality	pH	Dias- tase	Typ sin	Nonprotein Nitrogen	Sediment	Microscopic Observations	Smear	Cultures	Gastric Analysis	Roentgen Ry	Diagnosis	Remarks
1	A Yellow B Dark C Light	Clear Clear Sl turbid		66 64 96 35 76 80	12 50 10 52 5 23	35 59 47	++ ++ ++	Crystals 0 Crystals +	Same W B C	No growth	F A, 35 T A, 47	Negative	Psychoneurosis	
2	A Yellow B Dark C Light	Clear Clear Clear	6.8 4.6 5.8	53 32 36 36 36			++ ++ ++	Crystals 0 Crystals	Same 0 Same	Staphylococcus, colon	F A, 45 T A, 60	Spastic GI tract	Spastic colitis	
3	A Yellow B Dark C Light yellow	Clear Clear Turbid		10 11 6 25 0		33 31 26	++ ++ +++	Few crystals Hexagonal Crystals, W B C +++	Same Same W B C ++	Staphylococcus, ovoid gram + cocci, gram 0 streptobacillus, gram 0 thin bacilli	F A, 26 T A, 52	L R Q adhesions	Bant's dis- ease, pan- creatitis	Previous chole- cystectomy and chronic pancre- atitis at that time
3'	A Yellow B Black C Light yellow	Clear Clear Turbid	4.0 4.0 2.4	11 11 6 25 6 25		36 35 34	+						Same	
3''	A None B Dark C Light yellow	Clear Clear Turbid	7.0 2.4 2.4	6.04 0.0 0.0			0 ++ ++	Few W B C Crystals	W B C W B C	No growth	Not done	Carci- noma of stomach	Carcinoma of the stomach with liver metastasis	Died
4	A Yellow B Amber C Light	Clear Clear Turbid		33 33 71 42 0		Light Light Light	0 0 ++	± crystals ++	Pus			Negative	Chronic bili- ary disease	
5	A Yellow B Dark C Yellow	Clear Clear Clear	8.2 6.8 6.4	42 6 62 84 49 72		22 5 Pp+ Pp+	++ ++ +	Few crystals Few crystals Few crystals	W B C	Nonhemolytic strep, gram 0 bacillus				
6	A Yellow B Amber C Light yellow	Clear Clear Turbid	3.8 6.4 1.4	0.89 53 32 0.0	9.23 18 91 2.23	Too light Light	++ ++ +++	Crystals Crystals Crystals +++	W B C ++	Staphylococcus	T A, 26 T A, 50	L R Q adhesions	Chronic bili- ary disease	
7	A Yellow B Black C Yellow	Clear Clear Sl turbid	6.6 4.4 3.6	38 40 10 46 0.0	38 20 50 46 49 72	Pp+ Pp+ Pp+	++ ++ ++	Crystals Cholesterol Mucus crystals	0 W B C	Staphylococcus, colon, gram + ovoid cocci	F A, 56 T A, 66	Negative	Gallstones, chronic bili- ary disease	
8	A Yellow B Dark C Light yellow	Clear Clear Turbid		80 5 83 62 90 26		9.3 31.9 6.4	++ ++ +++	Debris Occ W B C Lambli	W B C ++	Colon pure	F A, 18 T A, 38	Negative	Chronic biliary infection, lamblia intestinalis	

[illegible]

TABLE 3—Results Obtained from the Examination of Fifty Patients—Continued

		Color	Quality	Diastase	Tryp- sin	Nonprotein Nitrogen	Sediment	Microscopic Observations	Smear	Cultures	Gastric Analysis	Roentgen Ray	Diagnosis	Remarks
20	A	Amber	Clear	42	246	618	+	Epl and crystals	Pus +	No growth	F A, 14 T A, 30	Negative	Chronic biliary disease	
	B	Dark	Clear	219	219	Spilled	+	Few crystals	0					
	C	Light yellow	Turbid	0	0	105	+++	Many crystals	Pus +++					
21	A	Yellow	Clear	2424			+			No growth	F A, 24 T A, 36	Negative	Gallstones	
	B	Dark	Clear	3821			±							
	C	Light yellow	Turbid	236			++++	+++ crystals	W B O					
22	A	Yellow	Clear	4122			±	0		Hemolytic streptococcus vaccine	F A, 40 T A, 62	Negative	Chronic biliary infection	
	B	Dark	Clear	68	6616		±	0						
	C	Amber	Clear	82	56		±	Few		Small gram 0 bacillus	F A, 22 T A, 48	R L Q adhesions	Migraine, chronic appendicitis	
23	A	Yellow	Clear	48	6366	23	+			Not done	Achylia	Negative	Carcinoma head of pancreas	Cholecystogram
	B	Dark	Clear	42	585	48	+							
	C	Yellow	SI turbid	36	510	18	++	Few Crystals	W B C W B C W B C	Not done		Negative	Chronic biliary disease	
24	A	Watery	Emulsified	0		Too light	+	Epithelial						
	B	Watery	Emulsified	0		Too light	+	Epithelial						
	C	Watery	Emulsified	0		Too light	+	Epithelial						
25	A	Yellow	Clear	636		1287	+	Epithelial						
	B	Dark	Clear	5234		2142	+	Crystals ±						
	C	Light yellow	Turbid	206		1605	++++	Crystals ++++	W B C					
26	A	Yellow	Clear	7166		1316	±	Epil and crystals		Nonhemolytic streptococcus	F A, 30 T A, 48	R U Q adhesions	Chronic biliary disease	
	B	Dark	Clear	6314		235	±	Crystals						
	C	Yellow	Clear	7166		1375	±	Crystals	W B C					
27	A	Yellow	Clear	6214		226	+	Epil and crystals		Staphylococcus, hemolytic streptococcus, vaccine, colon	F A, 28 T A, 40	Gallstones, reflex pylospasm	Cholelithiasis	
	B	Dark	Clear	9016		30	±	Crystals						
	C	Light yellow	Turbid	100		21	+++	Crystals +++	W B O					
28	A	Yellow	Clear	422		1626	+	Epil and crystals		Acrobates, 0, anaerobes, 0	F A, 30 T A, 31	Hypertonic G-I tract	Chronic biliary disease	
	B	Dark	Clear	1254		2742	+	Few crystals						
	C	Light yellow	Turbid	116		15	+++	Crystals +++	W B O					
29	A	Yellow	Clear	620			+	Epithelial		Not done	F A, 25 T A, 48	Negative	Pyeloneurosis	
	B	Dark	Clear				+	Few crystals						
	C	Light yellow	Turbid				+++	Crystals +++	W B O					
30	A	Yellow	Clear	5762			+	Crystals		No growth	F A, 42 T B, 64	Negative	Gallstones	
	B	Black	Clear				+							
	C	Yellow	Clear				+							

No.	Specimen	Color	Reaction	Microscopic	Gram	Culture	Pathology
31	A B O	Yellow Dark	Clear	90 20 56 21 69 8 33	Epithelial Few crystals	W B O	Chronic biliary disease
32	A B O	Yellow Dark	Clear	51 76 8 50 8	Crystals Crystals + + +	Bacterial W B O	Chronic appendicitis, proctitis, cystitis
33	A B O	Yellow Dark	Clear	91 10 103 32 97 12	Epithelial W B O Crystals	Bacterial W B O	Psychoneurosis
34	A B O	Yellow Dark	Clear	18 32 109 08 28 20	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease
35	A B O	Yellow Dark	Clear	58 16 63 50 19 28 18 22 22	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease
36	A B O	Yellow Dark	Clear	11 104	Epithelial Crystals	Bacterial W B O	Chronic biliary disease
37	A B O	Yellow Dark	Clear	22 0	Epithelial Crystals	Bacterial W B O	Chronic biliary disease
38	A B O	Yellow Dark	Clear	51 1 35 14 1 45 12 0	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease
39	A B O	Yellow Dark	Clear	80 76 59 81 86 32	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease
40	A B O	Yellow Dark	Clear	81 50 6 56 100 13 28 10 46	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease
41	A B O	Yellow Dark	Clear	16 10 32 67 50 25 19 13 11	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease
42	A B O	Yellow Dark	Clear	70 1 28 10 1 28 50 51 52 16 12 06	Epithelial Crystals Crystals	Bacterial W B O	Chronic biliary disease

TABLE 3—Results Obtained from the Examination of Fifty Patients—Continued

	Color	Quality	pH	Days fast	Tryp- sin	Nonprotein Nitrogen	Sediment	Microscopic Observations	Smear	Cultures	Gastric Analysis	Roentgen Ray	Diagnosis	Remarks
13	A	Yellow	4.6	24 04	11 30		+	Epi. lympho Crystals	W B C, bacteria 0	Hemolytic streptococcus	F A, 28 T A, 36	Nega- tive	Psycho-neurosis	
	B	Dark	4.6	46 26	16 52		+++	Crystals +++	Bacteria, W B C +++					
	C	Light yellow	1.3	14 16	10 26			Crystals +++						
14	A	Yellow	5.4	21 72			+	Crystals		Large gram + ovoid coccus, small gram 0 bacillus	F A, 27 T A, 49	Viscerop- tosis	Psychoneurosis	
	B	Black	5.8	33 21			+++	Crystals +++	W B C	Not done				
	C	Yellow	4.6	0				Crystals +++						
14	A	Yellow	5.4	33 33			+	Crystals	W B C			Same	Psychoneu- rosis	Repeated the following day
	B	Light yellow	2				+++	Crystals	W B C					
	C	Yellow	5.0				+	Crystals	Ooc W B C					
45	A	Yellow		23 37			+	Epithelial	Cells	No growth from A	F A, 21 T A, 43	Nega- tive	Chronic biliary infection	
	B	None							Many W B C					
	C	White												
46	A	Yellow	5.8	11 10	12 26	21 45								
	B	None												
	C	Light yellow	2.6	1 2	6 14	15 15	+++	Crystals +++	W B C, bacteria Epithelial Pus	Large gram + ovoid coccus	R A, 23 T A, 54	Nega- tive	Gallstones, chronic biliary disease, syphilis	Tubercu- lous
47	A	Yellow	6.4	12 03	16 03	20 40	+			Not done				
	B	Dark	6.2	16 33	2 33	42 87	+	Mucus						
	C	Light yellow	1.8	12 29	12 29	Too light	+++	Mucus, crystals						
17	A	Yellow	6.0	65 64	11 30	12	+			Colon, non hemolytic strep- tococcus	F A, 16 T A, 33	Nega- tive	Gallstones, chronic biliary disease	
	B	Amber	5.8	50	Too light	15	±							
	C	Light yellow	3.8	25	2 70	17 17	+++	Crystals +++	W B C					
18	A	Yellow	4.6	15 22			±	Few crystals		Not done	F A, 10 T A, 22	Nega- tive	Gallstones	
	B	Black	6.2	18 88			±	Few crystals						
	C	Yellow	5.3	13 62			±	Few crystals	W B C					
49	A	Yellow		Not done	40 00		+	and few crystals		Not done	F A, 17 T A, 31	Nega- tive	Syphilitic hepatitis	
	B	Black	4.7	53 32			±	Few crystals						
	C	Light yellow	1.9	12			+++	Crystals	W B C +++					
50	A	Yellow	6.0	96 00			±	Few crystals		Colon	F A, 18 T A, 26		Gallstones	
	B	Black	6.2	32			±	Few crystals						
	C	Light yellow	5.6	28 56			±	Few crystals						

In several cases, however, when B bile gave the normal reading, a considerable number of feathery flocculi were seen within the microscope. This will be discussed more at length.

Frequently considerable mucus appears, I feel that a great deal of this must be from the stomach.

*Microscopic Observations*—Both fresh and stained preparations were used. For the latter, one of the Romanowsky stains was employed, either Wilson's or Wright's. This stains the crystals well and outlines the cells clearly.

I have given a few results taken from a portion of our laboratory records. These are typical of the different kinds of bile.

#### COMMENT

It is common knowledge that typical B bile can be obtained from patients whose gallbladders have been removed. The observations of Dunn and Connell<sup>26</sup> carried out on a patient with a hepatoduodenostomy, without either gallbladder or common duct, are extremely suggestive. As this patient had a duodenal fistula, they were able to watch the response of the biliary secretion to different stimuli. They obtained the typical A, B and C fractions following magnesium sulphate stimulation and believe that this was caused by a reaction of the liver to the presence of magnesium in the portal blood. I, on the contrary, obtained B bile without other stimulation than having the tube in the duodenum.

With the foregoing facts before him, plus the observations of Bambridge and Dale,<sup>5</sup> Auster and Crohn,<sup>7</sup> Diamond<sup>8</sup> and others, Dr C. M. Jones<sup>22</sup> asserts that B bile does not come from the gallbladder. "The most likely explanation of its source would seem to be that it occurred during that period of time when the flow into the duodenum was the most rapid after the widest opening of the sphincter of Oddi following magnesium sulphate. As soon as the relaxation of the duodenum and sphincter diminishes, the flow of bile also diminishes, and the amount of bile pigments per unit volume of duodenal contents is correspondingly lowered. Subsequent fractions are therefore lighter in color, although repeated installations of magnesium sulphate will produce continued increases in pigment."

From the observations on the hydrogen ion concentration of the various fractions and the concomitant estimation of the pancreatic activity in the present experiments, I cannot concur in this dilution hypothesis. Usually when the C bile remains clear and has therefore a relatively high  $p_H$ , a diastase reading is obtained that is practically

<sup>26</sup> Dunn, A. D., and Connell, K. Hepatoduodenostomy with Observations on the Lyon-Meltzer Method of Biliary Drainage, *J. A. M. A.* **77** 1093 (Oct. 1) 1921.

similar to or slightly less than that found in B. If the change in pigmentation is the result of a pure process of dilution, surely the same action would also greatly reduce the concentration of the pancreatic juice. Anrep, Lush and Palmer,<sup>27</sup> and Mellanby<sup>28</sup> have shown that there is always a downward trend in the strength of enzyme secreted following a single or prolonged stimulation of secretion, and with the marked change in color caused by dilution, a marked change in enzyme activity would be expected.

Lyon accounts for the dark B bile in patients who were cholecystectomized by the concentration of the bile in the dilated ducts. If a remnant of the gallbladder was left, it might hypertrophy enough to assume this function of concentration. The Rockefeller<sup>29</sup> investigators have shown clearly that the action of the duct system is one of dilution, and that in the absence of the gallbladder, one is likely to obtain a more dilute than concentrated bile.

In more than a hundred drainages I have never seen a transfer from an A bile directly into a clear C bile. It always becomes the turbid light colored bile evidently called C that can be turned into the accustomed B simply by changing the hydrogen ion concentration. This of course prohibits the diagnosing of a pathologic gallbladder or occluded cystic duct.

So far there has been no convincing work that will definitely explain the various bile fractions. When one sees the dark viscid B bile come pouring out, it is difficult not to think that it originates at least partly in the gallbladder. Still, in view of a great deal of the work presented in the foregoing, this cannot be stated as a fact, and here the question must remain unsolved temporarily.

The estimations of biliary nonprotein nitrogen made by my co-workers and myself have been of no help in localizing the origin of the B bile, nor have we been able to find any connection between the amount of B and the nonprotein nitrogen. When large amounts were excreted, the finding of a lower nonprotein nitrogen might point to origin in the gallbladder with considerable dilution in its passage to the outside. This does not happen consistently.

The question of the interpretation of sediment in the bile is a difficult one. Most writers seem to consider the finding of it as an indication that some pathologic condition exists in the gallbladder or ducts. Many of them lay stress on the importance of finding it in increased amount.

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27 Anrep, G. V., Lush, J. L., and Palmer, M. G. Observations on Pancreatic Secretion, *J. Physiol.* **59** 434 (March) 1925.

28 Mellanby, J. The Mechanism of Pancreatic Digestion, the Function Secretin, *J. Physiol.* **60** 85 (May) 1925.

29 Rous, P., and McMaster, P. D. Physiological Cause for the Varied Character of Stasis Bile, *J. Exper. Med.* **34** 75 (July) 1921.

in patients with cholelithiasis. That considerable quantities of the bile crystals salts will precipitate out in the icebox is well known. Cholesterol will also crystalize out in such conditions, and, as cited in the foregoing, one can gradually increase the precipitation of like crystals, calcium carbonate and calcium bilirubinate simply by the process of gradually lowering the  $p_H$ . They do not pop out suddenly. I have found the least sediment in the tubes with the highest hydrogen ion concentration. A small amount of previous alkalization of these specimens does not prohibit the deposit of all this sediment on centrifugalization.

Perhaps the work of Rous, McMaster and Drury<sup>30</sup> have considerable bearing on this subject. By placing small glass cannulas in the hepatic or common duct of dogs with intact gallbladder, they found a deposit of small stones on the tubing. They also instituted continuous drainage by their method of placing a cannula in the duct and conducting the bile outside after going through a U of rubber tubing which lies in the animal's abdominal cavity and is surrounded by omentum. They found deposits of small stones along the glass and rubber tubing, the calcium bilirubinate deposit always lying nearest the duct and the calcium carbonate being found for a considerable way down the tube even when the drainage remained sterile. They always found a sediment in the bulb in which they collected the twenty-four hour specimens. The carbonate stones are always built up around a matrix of organic debris. They believe that there is a marked tendency for precipitation of pigment from normal bile. They also found in sterile bile, from the second to the sixth day after operation, a slight brown greenish, dustlike powder. Under the microscope it tends to assume a spherical form, sometimes in chain form, I have at times found it grouped together in a sphere having the appearance of a bile stained lymphoid nucleus. Just how much influence the rubber tubing has on this tendency of precipitation of crystals from human bile is unknown. The New York writers were unable to find any relation between the incidents of these nuclei or feathery crystals and the hydrogen ion concentration. I have been impressed by the association of increasing amounts of this feathery residue with a decrease in the  $p_H$ .

Whatever the cause, I cannot accept in a serious manner any interpretation of pathologic biliary change in reference to the finding of larger or smaller amounts of like pigment. In only two cases have I seen cholesterol crystals. Even the finding of these is not evidence of stone formations.

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30 Rous, P., McMaster, P. D., and Drury, D. R. Observations on Some Causes of Gallstone Formation, I, *J. Exper. Med.* **39** 777 (Jan.) 1924, Observations on Some Causes of Gallstone Formation, II, *J. Exper. Med.* **39** 97 (Jan.) 1924.

As to the possibility of obtaining bacterial growth that can be taken as representative of the infecting biliary organism, it may be done, but to have any assurance that it is so requires great faith. The examination of the later portions of the drainage when the bile has practically ceased to flow, and the appearance of a huge number of bacteria will destroy the hope in the minds of all but the most trusting. A great deal of work has been done on this question by Boardman,<sup>31</sup> who feels that it is a waste of time. Whipple,<sup>32</sup> using an especial technic, concludes that the finding of colon bacilli, the hemolytic streptococcus and *Staphylococcus aureus* after stimulation with magnesium sulphate designates their true biliary origin. I cannot agree with this. In patients with arthritis, when all else has been tried, the finding of a hemolytic streptococcus in the B bile fraction only may justify one in trying a vaccine. I did so in four cases. It is a short time since this was done, but I am not hopeful. That the bile is infected at times I do not doubt.

The finding of parasites in the return is, of course, of great diagnostic help. In only one patient of this series was *Lambia intestinalis* found.

This leaves for diagnostic help only the finding of pus cells and bile thrombi. My feeling concerning the importance of leukocytes is varied. Certainly their appearance in the turbid C fraction is of no value. Their appearance in a clear dark B bile of high  $p_H$  I think is more important, especially since it is so rarely seen. If this B bile is followed by a clear transparent C bile also with a high  $p_H$  in which about the same number or fewer cells are found, I think that it may be of some diagnostic significance. Bile thrombi which resembled urinary casts both in size and in appearance were infrequently seen. They are similar to those described by Naunyn.<sup>33</sup> Aschoff<sup>34</sup> insists that they are found in normal bile. The Rockefeller observers found them only in the contaminated sediment. The combination of these with white blood cells I consider an indication of hepatic pathologic change.

#### CONCLUSIONS

1. As a diagnostic procedure, medical drainage of the biliary duct is of relatively little value. (a) The origin of B bile is unknown. (b) Biliary sediment has no practical diagnostic significance. (c) The appearance of white blood cells is of relatively small help. They are

31 Boardman, W. W. A Study of the Bacteriological Findings in the Lyon-Meltzer Test, *Am J M Sc* **167** 847 (June) 1924.

32 Whipple, A. O. Use of the Duodenal Tube in Preoperative Study of the Bacteriology and Pathology of the Biliary Tract and Pancreas, *Ann Surg* **73** 556 (May) 1921.

33 Sydenham. A Treatise on Cholelithiasis, *M Soc Tr*, London, 1896.

34 Aschoff, L. Lectures, New York, 1924.

of value only in B bile of high  $p_H$  when this is followed by a C bile of high  $p_H$  (d) Bacteriologic studies are valueless and may lead one to place an incorrect estimation (e) Bile thrombi have a definite pathologic significance

2 Turbid C bile may be changed to a clear dark B bile by raising the hydrogen ion concentration The converse of this is also true

3 The finding of parasites is of great importance

4 The total absence of biliary secretion and the presence of pancreatic enzymes is a great help in the differential diagnosis of choledocholithiasis and carcinoma of the head of the pancreas

5 On account of the high pancreatic activity in most cases of gallstones and the production of gallstones in sterile tubes inserted into biliary tracts, I cannot feel that they have any connection per se with diabetes

# MINERAL SALT CONTENT OF THE BLOOD IN DISEASE \*

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This investigation was undertaken primarily as a clinical application of the work of Rohdenburg and Kiehlbiel<sup>1</sup> on the effect of the removal of ductless glands in rats on the salt content of the blood. The fact that parathyroid deficiency is definitely associated with a low content of blood calcium also suggested a possible deficiency of other mineral salts in diseases of other ductless glands.

In the course of the investigation we soon found, however, that the relationship between the salt content of the blood and the disturbances of the ductless glands that came under our observation was not constant. We therefore extended the work to include all the clinical conditions at our disposal in the medical service at the Lenox Hill Hospital.

We studied as controls the patients on the surgical service who were admitted for some minor surgical condition, such as hemorrhoids or hernia, and who apparently were free from systemic disease. There are few studies in the literature of the mineral content of the blood in either the normal or the diseased person. In order to establish normals and to evaluate our statistics, we grouped our observations according to the minimum and maximum figures obtained, since the number of patients free from disease was entirely too small to use as normals. We considered the figures which occurred in the majority of the cases as the average normal. If certain diseases were regularly grouped in large numbers either below the lowest level or above the upper level, these figures could be considered of pathologic significance for these diseases. If various diseases were associated regularly with constant low or high figures, we attempted to establish a common factor in these diseases to account for the abnormal figures obtained.

## METHOD

The specimen of blood was obtained in the morning before breakfast. About 30 cc of blood was taken from the median basilic or median

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\* From the Medical Service and the Achelis Laboratory of the Lenox Hill Hospital.

<sup>1</sup> Rohdenburg and Kiehlbiel. On the Relation of Certain Endocrines to the Salt Content of Rat Blood, *J. Cancer Research* 9:422 (Sept.) 1925.

cephalic vein at the elbow, in a bottle containing lithium citrate to prevent clotting. The determinations were made on whole blood because of the desire to obtain the figures for potassium, as well as for other mineral salts in the same specimens of blood. The sodium content was determined by the Kramer and Gittelman method<sup>2</sup> and the calcium and potassium content by the Kramer and Tisdall method<sup>3</sup>. The magnesium content was determined by a method devised by Bernhard<sup>4</sup>. This method consists of a combination of the precipitation of ammonium magnesium phosphate as described by Hammett and Adam,<sup>5</sup> and the colorimetric determination of phosphorus as described by Benedict and Thies.<sup>6</sup>

We determined the content of all the mineral salts and chlorides in all the cases of our series. The total salt content in each case was obtained by adding the figures of all the salts. The determinations of the mineral salts given in the literature were usually made on different groups of patients, and in none of the investigations were all the salt contents determined on the same patient.

We believe that this is the first series of cases in which all the salt contents were determined on the same patient.

We attempted to establish the following facts: (1) the average normal figures for each mineral constituent, (2) the average figures for the total amount of salts, (3) the relation of the figures obtained for each salt to the percentage which this constitutes of the total salt content, (4) the relation of the various salts to one another, for example, the relation of the sodium content to the potassium content, and the magnesium to the calcium content, and (5) the absolute and percentage content of the various salts and their relation to one another in various diseases.

We analyzed the blood of one hundred and seventy-three cases and determined the sodium, potassium, calcium, magnesium, chloride and total salt content. After determining the quantities per hundred cubic centimeters of blood, we calculated the percentage that these figures constitute of the total salt content.

*Sodium*—The sodium content of the blood varied from 51.8 mg. per hundred cubic centimeters of blood to 463 mg. We considered the average normal to be from 120 to 180 mg. These figures were obtained in one hundred and twenty-five of the one hundred and seventy-three

2 Kramer and Gittelman. *J. Biol. Chem.* **62**: 353 (Dec.) 1924.

3 Kramer and Tisdall. *J. Biol. Chem.* **48**: 223 (Sept.) 1921.

4 Bernhard, A., and Beaver, Jacob J. *J. Biol. Chem.* **69**: 113 (July) 1926.

5 Hammett and Adam. *J. Biol. Chem.* **52**: 211 (May) 1922.

6 Benedict and Thies. *J. Biol. Chem.* **61**: 63 (Aug.) 1924.

cases Compared with Kramer and Tisdall's <sup>7</sup> figures, our determinations are considerably lower, since the figures given in their article are from 187 to 195 mg

*Potassium*—The potassium content of the blood varied from 28 to 229 mg per hundred cubic centimeters of blood We considered the average normal from 130 to 170 mg, which were the figures obtained in one hundred and nineteen out of one hundred and seventy-three cases Kramer and Tisdall,<sup>7</sup> in a much smaller group of cases, obtained figures from 164 to 200 mg per hundred cubic centimeters These are considerably higher than our figures

*Calcium*—Our figures for calcium on whole blood determinations varied from 3 to 13 mg per hundred cubic centimeters In one hundred and fifteen of the cases we obtained figures from 6 to 11 mg per one hundred cubic centimeters, and we considered these as the average normal They are somewhat higher than those obtained by Kramer and Tisdall <sup>7</sup> in whole blood

*Magnesium*—The magnesium content of the blood varied from 1 to 5.8 mg per hundred cubic centimeters We considered the average normals from 2.98 to 4 mg, which was obtained in one hundred and eleven of the cases

*Total Amount of Salts*—The total salt content of the blood, which was obtained by adding the figures for sodium, potassium, calcium and magnesium, varied from 224 to 551 mg per hundred cubic centimeters, the average figures ranging from 250 to 300 mg

#### PERCENTAGE CONTENT OF MINERAL SALTS

*Sodium*—The percentage content of sodium varied from 17.7 to 84.2 per cent In one hundred and one cases it was from 40 to 55 per cent, which we considered the average normal

*Potassium*—The percentages for potassium varied from 10.2 to 78.3 per cent In one hundred and seventeen cases the range was from 35 to 45 per cent, and we consider these figures the average normal

*Calcium*—The percentage of calcium varied from 0.9 to 4.8 We consider the normal to be from 2 to 3.5 per cent, which were the figures obtained in the majority of cases

*Magnesium*—The magnesium percentage ranged from 0.2 to 2.4 We consider the normal figures to be from 1 to 1.5 per cent, which were the figures obtained in one hundred and twenty-seven of the cases

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<sup>7</sup> Kramer and Tisdall The Distribution of Sodium, Potassium, Calcium and Magnesium Between the Corpuscles and Serum of the Human Blood, J Biol Chem **53** 241 (Aug) 1922

## THE RELATION OF ABSOLUTE AND PERCENTAGE FIGURES

The comparison of the percentage figures with the absolute figures, as shown in the table, indicates that the percentage of each salt content does not vary constantly from its absolute content, in other words, when the content of a mineral constituent is increased or diminished, its percentage of the total salt is also correspondingly increased or diminished. A study of the table also indicates that there is a reciprocal relationship between sodium and potassium. Whenever the sodium content of the blood or its percentage of the total salt is increased, the potassium content is correspondingly low, and vice versa. There was no relation between the calcium and magnesium content. As a rule, a low magnesium content was associated with a low calcium content, but this was not a constant phenomenon. The magnesium content, however, showed less tendency to vary than the calcium.

## PATHOLOGIC OBSERVATIONS

The pathologic observations may be divided into three groups (1) diseases associated with the minimum figures, (2) diseases associated with the maximum figures and (3) the mineral salt content in specific diseases.

*Sodium* —While the data are not striking, ten of the cases of goiter with hyperthyroidism were associated with a low sodium content, as were six of the cases of simple goiter. We also find ten cases of goiter among the lowest normal figures.

The highest figures for the sodium content were present in leukemia purpura hemorrhagica, and chronic nephritis with hypertension.

The association of the various diseases with the minimum and maximum figures was apparent both in the percentages and in the absolute figures. The association of goiter with the lower percentages was not so apparent. In the maximum figures, however, both the absolute and the percentage determinations coincided in the various disease groups.

*Potassium* —The lowest figures for potassium, both in the absolute and in the percentage determinations, occurred in the cases of leukemia and purpura hemorrhagica, and were remarkably low. These low figures are probably not specific for these diseases, but were merely the result of the progressive loss of blood, since both cases were extremely severe and the patients had considerable hemorrhage. The potassium is contained principally in the corpuscles, and the marked reduction in the percentage of potassium is probably due to the reduction in the number of the corpuscles as the result of the continued hemorrhage. The low potassium content was associated with a marked increase in both the absolute and the percentage content of the sodium.

TABLE A—Mineral Salt Content in Various Diseases

Name	Diagnosis	Basal Metabo- lism, per Cent	Sodium	Potash	Magne- sium	Chl- cium	Chlorine	Total Salts	Sodium, per Cent	Potash, per Cent	Magne- sium, per Cent	Cal- cium, per Cent
GOITER												
M P	Goiter with hyperthyroidism	+89	140.9	136.0	2.7	4.9	544.0	285	49.4	47.7	1.0	1.9
A F	Goiter with hyperthyroidism	+72	148.0	139.9	1.96	4.3	478.0	294	50.3	47.6	0.9	1.2
M H	Goiter with hyperthyroidism or toxic adenoma	+18	122.4	134.9	2.33	6.1	485.1	265	46.0	50.9	0.9	2.2
A R	Goiter with hyperthyroidism	+16	182.8	119.99	2.33	7.5	484.9	313	58.4	38.3	0.9	2.4
M B	Exophthalmic goiter or toxic adenoma	+97	186.16	144.13	2.8	8.2	534.6	341	54.5	42.2	0.9	2.4
A H	Goiter	+14	136.2	141.29	2.1	4.2	469.0	283	48.0	49.8	0.9	1.3
A U	Goiter with hyperthyroidism or autonomous disturbance	-0.3	142.33	125.67	2.74	6.5	442.2	278	51.0	45.3	1.0	2.7
R I	Artificial menopause, goiter	+28		140.58	2.55	7.0	448.8	280	45.3	51.4	1.0	2.3
E H	Goiter	+31	126.95	143.78	3.41	6.4	465.3	252	46.8	49.5	1.0	2.7
A M	Goiter with hyperthyroidism	+35	117.85	124.61	3.02	5.5	486.8	267	47.9	48.6	1.1	2.4
F S	Goiter	+11	128.1	130.29	2.90	5.5	491.7	500				
S M	Exophthalmic goiter with residual symptoms	+8	180.5	135.3		7.8						
J D	Goiter with hyperthyroidism		153.7	133.13			478.5	328	51.8	44.8	0.9	2.4
M G	Goiter with hyperthyroidism (old cured case)		169.65	146.49	2.98	8.2	503.3	336	48.8	48.2	0.86	2.1
L G	Goiter with hyperthyroidism or autonomous symptoms		163.96	162.24	2.86	7.1	528.5	322	51.5	44.7	1.2	2.5
P	Goiter with hyperthyroidism		166.2	144.1	3.0	8.2						
M D	Goiter with mild hyperthyroidism		134.9	147.7	3.9	7.1	536.3	294	45.1	50.3	1.3	2.4
S	Goiter with hyperthyroidism		136.1	143.2	3.5	8.2	511.5	291	46.7	49.7	1.2	2.8
L	Exophthalmic goiter, recurrence, after partial thyroidectomy											
D	Goiter with hyperthyroidism		148.2	167.6	4.7	7.3	503	319	46.7	49.5	1.4	2.3
L S	Goiter with nervous symptoms		146.3	164.7	3.5	9.8	495	325	44.9	50.7	1.7	3.0
F S	Hyperthyroidism with gastric symptoms		97.92	146.3	4.3	7.7		256	38.2	57.0	1.6	3.0
W S	Goiter		135.5	109.7	3.9	7.6	524.7	257	52.0	42.8	1.5	2.9
A S	Postoperative goiter and hyperthyroidism		183.9	139.9	3.1	6.7	491.7	331	55.7	42.3	0.9	1.1
G O	Goiter, simple		118.0	140.0	4.19	6.5	471.9	300	49.6	46.0	1.3	2.6
I S	Goiter		141.18	130.29	3.02	7.0	486.8	311	51.0	46.2	1.1	2.6
H H	Goiter		161.5	136.7	2.74	6.7	470.3	314	52.6	40.7	0.9	5.8
R W	Goiter		166.24	123.9	2.4	8.3	504.9	300	55.5	41.3	0.9	2.3
H W	Goiter with hyperthyroidism		97.92	110.09	2.94	6.5	506.6	224	43.7	57.8	1.2	3.3
L R	Hyperthyroidism or neurosis	+10	101.9	117.15	3.25	6.9	486.8	239	44.5	51.0	1.2	3.3
V S	Adolescent goiter	-1	119.55	123.87	2.7	6.3	481.8	258	46.5	50.0	1.1	3.4
A F	Postoperative goiter	+9	124.68	166.50	3.02	6.3	440.1	301	41.5	55.1	0.9	2.2
B H	Postoperative goiter	-8	154.28	123.29	4.10	6.8	483.3	288	53.4	42.7	1.4	2.9
L S	Hyperthyroidism or neurosis	+8	98.49	129.93	3.29	6.4	483.3	237	40.9	54.8	1.2	3.1
T R	Goiter (menstruating at the time)	-4	129.4	129.2	3.13	6.7	452.1	261	46.8	49.3	1.1	2.8
E B	Goiter	+9	115.0	129.93	3.25	7.1	471.9	275	45.0	50.9	1.1	3.0
A C	Goiter with hyperthyroidism	+3	152.57	151.94	3.49	7.2	490.7	315	48.5	48.1	0.9	2.5
E S	Hyperthyroidism or neurosis	+0.2	143.46	118.57	3.45	6.8	272	272	52.6	43.7	1.0	2.7
M H	Hyperthyroidism or neurosis	+7	204.38	198.45	2.77	3.7	529	409	49.8	48.4	0.9	0.9
A H	Goiter with hyperthyroidism		141.18	143.78	2.19	6.3	463.6	236	40.6	56.2	0.9	2.3

			-S +34	123 4	142 71 149 8	294 3 25	71 6 8	475 2 455	284	437	52 8	1 0	2 5
L F	Adolescent goiter with hyperthyroidism												
B C	Latent hyperthyroidism with goiter and hypertension												
I S	Menopausal goiter, nervous symptoms, artificial menopause, ovaries removed four years ago		223 7	97 5	3 8	11 5	561	336	66 6	28 8	28 8	1 1	3 1
I R	Goiter with hyperthyroidism, improved		168 8	129 6	2 4	7 6	511 5	306	54 5	42 4	42 4	0 2	2 1
II H	Goiter with hyperthyroidism		148 0	157 6	5 1	7 8	495	318	46 5	49 6	49 6	1 5	2 1
II H	Postoperative goiter and diabetes		171 4	142 7	1 1	7 6	503 3	326	52 4	43 8	43 8	1 2	2 3
EFFECT OF THYROIDECTOMY ON SALT CONTENT OF THE BLOOD													
Y W	Goiter with hyperthyroidism	Before operation	+17	171 8	157 2	3 0	6 5		338	50 7	46 4	0 8	1 9
		One week after		171 8	156 5	3 2	7 0		338	50 8	46 0	0 9	2 0
BLOOD DISEASES													
W	Leukemia (two determinations about a month apart)		240 2	28 8	2 9	13 7	561 0	285	81 2	10 2	10 2	1 0	4 4
M F	Purpura hemorrhagica and splenectomy		163 4	71 6	3 1	9 8	300 0	551	84 0	13 6	13 6	0 6	1 8
			217 5	113 6	2 82	8 5	465 3	313	63 5	33 2	33 2	0 81	2 1
CARCINOMA													
H	Carcinoma of liver and diabetes		115 57	117 5	2 7	5 6	488 4	243	47 7	48 5	48 5	1 2	2 6
F N	Mediastinal tumor, malignant, probably carcinoma		192 9	134 9	3 1	7 2	511 5	338	57 1	39 8	39 8	0 9	2 2
F O	Carcinoma of stomach, postoperative		139 5	117 15	3 1	8 9	544 5	270	51 8	43 3	43 3	1 4	3 3
I	Carcinoma of the bladder		205 0	102 6	3 7	9 7	536	321	63 9	32 1	32 1	1 1	3 0
L O	Neoplasm of lung or chronic pneumonitis		136 7	134 5	4 1	7 6	478 5	283	48 4	41 1	41 1	1 1	2 6
K	Epithelioma of cervix		116 7	171 8	4 0	8 9	495	301	32 8	57 1	57 1	1 3	2 8
No 107	Carcinoma		138 8	114 6	2 1	5 6		253	53 8	44 4	44 4	0 6	1 2
No 548	Carcinoma of the breast		187	229 7	2 1	5 6		427	43 8	53 8	53 8	0 5	1 4
No 626	Carcinoma of the breast		131 7	191 4	1 3	5 3		330	39 9	58 0	58 0	0 4	1 6
No 3161	Carcinoma of the rectum		156 6	131 3	1 8	5 0		237	52 7	44 2	44 2	0 6	1 7
No 1382	Carcinoma of the esophagus		170 8	149 7	1 23	4 6		307	49 1	48 8	48 8	0 4	1 5
No 1638	Carcinoma of the esophagus		181 6	154 5	2 41	4 8		344	52 8	41 9	41 9	0 7	1 4
No 3179	Carcinoma of the esophagus		143 8	116 5	2 42	4 6		269	53 1	43 3	43 3	0 9	1 7
No 4669	Carcinoma of the breast		208 5	191 8	2 0	5 3		108	51 1	47 0	47 0	0 5	1 3
No 4676	Carcinoma of the sigmoid		144 7	130 5	1 4	4 8		282	51 3	46 4	46 4	0 6	1 7
No 5166	Carcinoma of the breast		157 9	142 8	2 5	5 3		309	51 1	46 2	46 2	0 8	1 7
No 1790	Carcinoma of the stomach		153 8	129 8	3 8	5 6		295	52 8	14 0	14 0	1 3	1 9
NEPHRITIS													
M O	Acute nephritis		121 68	138 1	3 57	6 8	109 2	274	15 2	50 3	50 3	1 1	3 1
M L	Chronic nephritis, acute uremia, chronic cholecystitis, gallstones, came in com		161 11	137 4	3 21	8 1	132 3	309	52 1	41 3	41 3	0 97	2 6
L	Cardioneuritis		104 75	117 85	3 1	5 9		292	35 0	60 1	60 1	1 0	2 0
L G	Chronic nephritis, patient died		129 8	156 6	4 3	6 5		297	43 8	52 5	52 5	1 3	2 2
S F	Chronic nephritis with hypertension		159 4	116 8	4 1	5 7	511 5	286	55 5	40 9	40 9	1 4	2 0
O	Acute exacerbation of chronic nephritis		126 95	129 2	5 0	7 9	577 5	269	45 3	47 9	47 9	1 8	2 2
K K	Chronic nephritis		164 5	135 3	4 98	7 7	585 8	313	52 7	43 1	43 1	1 6	2 1
J S	Chronic nephritis, hypertension, chronic myocarditis and bronchopneumonia		195 2	98 7	3 6	9 7	495 0	307	63 5	32 2	32 2	1 1	3 1
D R	Chronic nephritis and hypertension		241 4	59 64	2 9	11 1	561 0	315	76 5	19 0	19 0	0 9	3 5

TABLE A—Mineral Salt Content in Various Diseases—Continued

Name	Diagnosis	Basal Metabo- lism, per Cent	Sodium	Potas- sium	Magne- sium	Oil clum	Chlorine	Total Salts	Sodium, per Cent	Potas- sium, per Cent	Magne- sium, per Cent	Cal- cium per Cent
HYPERTENSION												
E B	Essential hypertension		179.7	154	2.3			341	52.7	45.1	0.6	1.5
B C	Latent hyperthyroidism with goiter, hypertension	+31	123.4	140.8	3.25	6.8	455	284	43.7	52.8	1.0	2.5
H S	Menopausal hypertension		163.1	138.1	2.94	9.2	580.9	315	52.3	43.8	0.93	3.0
S F	Chronic nephritis with hypertension		169.4	116.8	1.1	5.7	511.5	286	55.5	40.9	1.4	2.0
S J	Chronic nephritis, hypertension, chronic myocarditis and bronchopneumonia		105.3	98.7	3.6	9.7	493.0	307	63.5	32.2	1.1	3.1
D R	Chronic nephritis, hypertension		241.4	59.64	2.9	11.1	561.0	315	76.5	19.0	0.9	3.5
G K	Gastric ulcer and hypertension		240.2	23.8	2.9	13.7	561	285	84.2	10.2	1.0	4.4
ARTERIOSCLEROSIS												
J B	General arteriosclerosis and senile psychosis		171.9	138.8	4.3	7.1	511.5	322	53.4	43.1	1.3	2.3
N G	Cerebral arteriosclerosis		169.9	145.9	3.2	8.5	486.8	267	41.2	54.7	1.2	3.1
H G	General arteriosclerosis and syphilis		125.2	138.1	4.3	7.8	519.8	275	46.5	50.1	1.5	2.7
THROMBO-ANGIITIS OBLITERANS												
I S	Diabetes and thrombo-angiitis obliterans		169.5	128.8	4.2	7.2	561	324	51.7	44.7	1.3	2.3
P H	Raynaud's disease		146.2	156.9	3.1	7.3	463.5	312	46.1	50.3	0.9	2.3
CARDIO VASCULAR DISEASE												
J K	Chronic cardiovascular disease, mitral stenosis, and aortic insufficiency		158.3	131.4	3.8	8.9						
B	Chronic myocarditis with decompensation		111.6	149.8	5.8	11.4		279	40.1	53.8	2.4	4.0
D	Chronic myocarditis and bronchopneumonia		151.4	147.7	3.6	7.8	528	311	48.6	47.6	1.1	2.5
W	Syphilitic ulcer and old endocarditis		150.0	171.8	3.4	6.1	463.7	339	46.6	50.7	1.0	1.8
S	Arthritis of left elbow and myocarditis		140.1	171.3	3.7	5.8	498.3	324	43.2	53.7	1.1	1.8
S J	Chronic nephritis, hypertension, chronic myocarditis and bronchopneumonia		195.3	98.7	3.6	9.7	495.0	307	63.5	32.2	1.1	3.1
GALLSTONES AND GALLBLADDER DISEASE												
F N	Pituitary dystrophy, pituitary headache, gallstones recently removed, obesity and cholecystitis		192.99	134.9	3.1	7.2	511.5	338	57.1	39.8	0.9	2.2
S	Obesity and cholecystitis		165.1	143.4	3.0	7.7	478.5	319	51.7	41.9	0.9	2.3
F	Jaundice		173.1	117.2	1.4	8.1		302	57.2	38.7	1.4	2.6
P K	Chirrhosis of liver and bronchopneumonia		158.3	131.4	3.8	8.9		302	52.3	43.3	1.2	2.9
M	Catarrhal jaundice		154.85	148.75	3.37	5.5	448.8	313	49.5	47.6	0.9	2.0
Y S	Chronic cholecystitis		152.0	164.4	3.37	9.4	478.5	330	46.0	49.7	0.9	2.7
S	Gallstones, headaches and palpitation		128.7	168.6	4.6	8.1	520.0	311	41.4	54.3	1.4	2.6
GASTRIC OR DUODENAL ULCER												
O K	Gastric ulcer and hypertension		176.5	147.7	3.3	9.5	470.3	337	52.5	43.9	1.0	2.9
O A	Duodenal ulcer		161.1	133.1	3.8	3.9	528.0	302	53.3	41.0	1.2	1.3
A S	Duodenal ulcer		105.9	107.21	4.5	8.1	462	286	37.0	58.4	1.5	2.8
A P	Gastric ulcer		158.3	155.1	3.9	5.6	463.8	322	49.0	48.1	1.2	1.7



TABLE A—Mineral Salt Content in Various Diseases—Continued

Name	Diagnosis	Basal Metabo- lism, per Cent	Sodium	Potas- sium	Magne- sium	Cal- cium	Chlorine	Total Salts	Sodium, per Cent	Potas- sium, per Cent	Magne- sium, per Cent	Cal- cium per Cent
DIABETES												
G	Diabetes	146.9	137.4	3.4	6.2	503.3	294	54.0	45.6	1.1	2.1	2.1
II	Diabetes and carcinoma of the liver	115.57	117.50	2.7	5.6	488.4	243	47.7	48.5	1.2	2.6	2.6
F D	Diabetes	141.6	142.0	3.3	7.7	544.5	298	48.6	47.6	1.1	2.6	2.6
M H	Diabetes and postoperative goiter	171.4	142.7	4.1	7.6	503.3	326	52.4	43.8	1.2	2.3	2.3
F W	Obesity and glycosuria	175.0	119.64	2.55	7.9	483.1	311	57.8	58.5	0.9	4.8	4.8
R F	Diabetes in an old lady	123.8	131.0	4.1	10.3		267	45.7	49.0	1.5	3.8	3.8
F H	Diabetes with cellulitis of right leg and thigh	88.8	168.3	3.8	8.1		269	33.1	62.4	1.4	3.3	3.3
I S	Diabetes and thrombo-angitis obliterans	160.5	138.8	4.2	7.2	561	324	51.7	44.7	1.3	2.3	2.3
OBESITY												
O S	Pituitary and ovarian obesity	129.8	133.13	4.39	7.1	480.2	274	47.4	48.5	1.4	2.7	2.7
F W (duplicate)	Pituitary obesity with glycosuria	176.9	119.64	2.55	7.9	485.1	311	57.8	38.5	0.9	4.8	4.8
F N (duplicate)	Pituitary dystrophy, obesity, pituitary headache, gallstones recently removed	192.93	134.9	3.1	7.2	511.5	338	57.1	39.8	0.9	2.2	2.2
S (duplicate)	Obesity and cholecystitis	165.1	143.4	3.0	7.7	478.5	319	51.7	44.8	0.9	2.3	2.3
R H (duplicate)	Pituitary dystrophy, obesity and epilepsy	165.66	144.84	2.98	7.9	495.0	321	51.7	45.1	0.9	2.4	2.4
DISEASES OF THE NERVOUS SYSTEM												
B	Hemiplegia	120.12	137.03	4.19	6.5	438.9	268	44.7	51.5	1.2	3.0	3.0
F	Neuralgia of sciatic nerve	136.63	128.51	3.37	7.0	478.5	276	49.7	47.4	1.1	1.8	1.8
W W	Syphilis and chorea	139.31	131.9	2.82	6.1	462.0	282	49.2	48.5	1.1	1.2	1.2
W V	Tabs	114.4	138.8	4.7	7.4	488.3	265	43.0	52.4	1.7	2.8	2.8
J B	General arteriosclerosis and senile psychosis	171.0	138.8	4.3	7.1	511.5	322	53.4	48.1	1.3	2.7	2.7
N G	Cerebral arteriosclerosis	109.9	145.9	3.2	8.5	480.8	267	41.2	54.7	1.2	3.1	3.1
No 721	Chorea						369	63.5	33.4	0.8	2.2	2.2
NEUROSES												
II G	Gastric neurosis with autonomic dysfunction symptoms and gastroptosis	126.4	140.94	2.5	4.0	445	274	45.9	51.4	1.0	1.7	1.7
M S	Autonomic dysfunction with asthenia	148.62	160.01	1.9	5.4	462.1	315	46.9	50.9	0.6	1.6	1.6
A T	Autonomic dysfunction following panhysterectomy	156.6	132.1	2.45	6.3	493.4	297	52.9	41.4	0.9	1.8	1.8
M L	Autonomic dysfunction, subnasal personality, gastric and rectal spasms	110.44	134.55	4.07	6.7	445.5	256	42.9	52.2	1.4	3.5	3.5
P	Gastric neurosis	115.57	117.50	2.70	1.6	488.4	243	47.7	48.5	1.2	2.6	2.6
H A	Neurosis, insomnia, veronal habit	134.0	137.74	3.1	7.0	455.5	288	48.5	47.7	1.1	2.6	2.6
D	Gastric neurosis	139.5	139.9	3.1	4.0	480.8	287	48.8	48.8	1.0	1.8	1.8
F S	Anxiety neurosis	104.2	198.8	5.3	6.0	445.5	314	33.1	63.3	1.6	1.9	1.9
R V	Neurosis, amenorrhea	152.7	117.86	3.36	7.1	509.7	281	54.5	42	1.1	2.5	2.5
EPILEPSY												
No 708	Epilepsy	145.35	155.14	1.53	3.98		306	47.5	50.7	0.5	1.3	1.3
No 683	Epilepsy	132.8	140.4	1.97	6.5		282	47.1	49.8	0.7	2.3	2.3
H S	Epilepsy	137.0	161	2.7	5.6		306.3	44.7	52.5	0.9	1.8	1.8
R H	Epilepsy, pituitary dystrophy and obesity	165.66	144.84	2.98	7.9	495.0	321	51.7	46.1	0.9	2.4	2.4

## HEADACHES

T O	Headaches, sinus involvement, possible pituitary headache	1253	1312	12	69	271	161	191	17	25
A B	Headaches, removal of cystic ovary	1094	1184	10	102	272	100	514	15	37
I B	Headaches, possible cerebrospinal syphilis	1719	1388	37	67	331	536	133	11	21
D	Panhysterectomy, artificial menopause and headaches	1571	1373	38	86	305	515	112	12	26
F S	Headache	16791	11147	353	82	291	577	384	12	28
F N	Pituitary dystrophy, obesity and pituitary headache, gallstones recently removed	19269	1319	31	72	338	571	398	09	22
H G	Pituitary headaches	1192	1216	26	66	283	526	138	11	25
ENDOCRINE CONDITIONS										
R H	Pituitary dystrophy with epilepsy	1651	11484	298	79	321	517	151	09	21
F N	Pituitary dystrophy, obesity with pituitary headache, gallstones recently removed	1929	1310	31	72	338	571	398	09	22
F W	Dwarfism	1566	12125	38	82	293	536	123	13	28
H	Eunuchoidism with pituitary headache, acromegalic characteristics	1123	1355	38	92	311	156	501	12	29
T K	Eunuchoidism	1133	12567	251	70	278	510	453	10	27
J F	Acute articular rheumatism, eunuchoidism	1197	1292	294	67	289	519	416	10	21
H G	Pituitary headache	1492	1216	20	66	283	526	138	11	23
MENOPAUSE CASES										
B	Menopause arthritis	1127	13987	279	50	261	133	536	11	20
F L	Menopause syndrome, myxedema?	1109	11342	31	65	294	479	189	10	22
K M	Menopause arthritis	13777	1455	268	57	293	470	499	10	21
A S	Menopause syndrome	1503	11297	329	56	302	193	173	10	21
M S	Menopause hypertension	1651	1381	291	92	315	523	138	093	30
I S	Menopause garter, nervous symptoms, artificial menopause, ovaries removed four years ago	2237	973	38	114	336	666	288	11	31
D	Panhysterectomy several years ago, headaches, artificial menopause	1571	1353	38	86	305	513	112	12	26
A B	Headaches, removal of cystic ovary	1094	1184	40	102	272	100	514	15	37
A T	Autonomic dysfunction and panhysterectomy	1566	1321	245	63	297	529	141	09	18
GYNECOLOGIC CONDITIONS										
S	Chronic salpingitis	9561	1285	191	118	241	394	344	13	32
L K	Retroflexed uterus and hemorrhoids	1719	956	37	91	282	609	168	13	27
W	Pyosalpinx	1526	1415	39	83	310	493	535	20	18
R V	Neurosis, amenorrhea	1527	11789	336	71	281	514	120	11	25
MISCELLANEOUS CONDITIONS										
P	Chronic constipation	1497	1518	18	92	319	170	186	15	29
W	Gastroptosis and hemorrhoids	1588	1516	38	98	321	190	460	11	30
O T	Hemorrhoids	1093	1412	15	110	266	409	530	16	11
K	Varicose veins at base of tongue with hemorrhages	1101	1617	56	100	297	390	535	19	13
S	Swelling and itching of the skin	1577	12316	349	71	296	530	432	10	28
O L	Hematuria, chronic tonsillitis, uncrupt third molar	9052	1239	260	69	223	104	551	12	23

*Calcium*—The lowest figures for calcium occurred in carcinoma. In acute and chronic nephritis, essential hypertension, chronic arthritis, acute articular rheumatism, goiter with hyperthyroidism, epilepsy and gastric neurosis the calcium content was also below the normal average figures.

The highest figures were found in leukemia. It is rather doubtful whether this is a specific phenomenon of the disease. It is probably a reaction of continued hemorrhage and an indication of the effort on the part of the body to maintain life, for which calcium, as well as sodium, is essential.

The occurrence of the low calcium figures in the cases of gastric neurosis and gastric ulcer was especially notable in the percentage figures. The significance of the low calcium content in these diseases is rather doubtful, because subsequent examinations of the calcium content in similar conditions on blood serum alone have given more normal figures.

*Magnesium*—Nearly all the carcinoma cases that we studied were characterized by the lowest magnesium figures in our entire series. This was apparent both in the absolute figures and in the percentages.

The highest figures occurred in arteriosclerosis, chronic arthritis, and disease of the gallbladder. These high figures may not be a specific phenomenon of these diseases, but merely a characteristic of old age.

*Total Amount of Salts*—In the diseases in which the mineral salt content was considerably changed from the average normal, tendency to hypermineralization, as shown by the increased salt content, was apparent. The highest figures for total salt content were obtained in carcinoma, leukemia, purpura hemorrhagica and disease of the gallbladder.

#### MINERAL SALT CONTENT IN SPECIFIC DISEASES

A study of the table indicates the mineral salt content of the blood in various diseases, as follows:

*Goiter*—In goiter with hyperthyroidism, ten cases showed low figures for sodium and occasionally for calcium. There was apparently no relation between the basal metabolic rate and the salt content of the blood. The figures are probably not significant.

*Diseases of the Blood*—The cases of purpura hemorrhagica and leukemia both showed a high figure for sodium, a low figure for calcium and a low figure for potassium, as well as a high total salt content. We do not think this is specific for these diseases but merely the reaction to severe and prolonged hemorrhage.

*Carcinoma*—In carcinoma, as is shown in the table, some striking figures were obtained. Nearly all the cases showed the lowest magnesium figures in our series, both in the absolute content and in the

percentage, as well as a tendency to hypermineralization. The low figure for calcium, however, was apparent in only about 50 per cent of the cases.

*Nephritis*—All the cases of chronic nephritis showed a low calcium and high chloride content when edema was present. Chronic nephritis with hypertension showed a high sodium content as well.

*Hypertension*—In essential hypertension the figures were not striking, although there was a tendency to low calcium figures.

*Arteriosclerosis*—The only observation in this disease was a high magnesium content, probably characteristic of old age.

*Gastric Ulcer and Gastric Neuroses*—The cases of gastric ulcer and gastric neuroses are grouped together, because of the similarity of the symptoms and constitutional manifestations. They showed a tendency to a low calcium and low magnesium content.

In ulcer, however, both the magnesium and the calcium figures were low. In carcinoma only the magnesium content was low, and the calcium did not show striking changes.

*Autonomic Dysfunction*—These cases showed a tendency to low magnesium and low calcium content.

*Disease of the Gallbladder*—Disease of the gallbladder was characterized by a tendency to a high calcium content and a characteristic lack of variability in the percentage of calcium. The magnesium and the total salt content were also high.

*Arthritis*—In the few cases of chronic arthritis and acute articular rheumatism in the series, there was a tendency toward a low calcium content.

*Epilepsy*—The few cases of epilepsy which we studied showed a low magnesium and low calcium content.

In all the other diseases given in the table, the figures are normal but not significant.

#### SUMMARY AND CONCLUSION

1 The mineral salt content of the blood was studied in one hundred and seventy-three patients suffering from various diseases.

2 The determinations were made on whole blood, both the absolute and the percentage figures being determined, as well as the total salt content.

3 The normal figures for the various salts were as follows:

<i>Absolute</i>	<i>Percentage</i>
Sodium, 120 to 180 mg per 100 cc	40 to 55 per cent
Potassium, 130 to 170 mg per 100 cc	35 to 45 per cent
Calcium, 6 to 11 mg per 100 cc	2 to 3 per cent
Magnesium, 2.98 to 4 mg per 100 cc	1 to 1.5 per cent
Total salts 250 to 300 mg per 100 cc	

4 There is no variation between the absolute salt content and its percentage of the total salts

5 A reciprocal relationship between the sodium and the potassium content of the blood was determined

6 The calcium and the magnesium content of the blood usually ran parallel

7 The most striking pathologic conditions in which a disturbance of the mineral salts in the blood was determined were carcinoma, leukemia and purpura hemorrhagica

8 In carcinoma there was a strikingly low magnesium content and a low calcium content in 50 per cent of the cases, but not so marked a tendency toward hypermineralization

9 In two of the cases of leukemia and purpura hemorrhagica which we studied, there was a marked reduction in the potassium content and a compensatory increase in the sodium and the calcium content, which we believe is probably due to hemorrhage

10 High magnesium contents were found in arteriosclerosis and in other conditions which usually are associated with advancing years

11 Chronic nephritis with hypertension showed a low calcium and a high sodium content

12 Disease of the gallbladder showed a high total salt and a high magnesium content

13 There were a number of tendencies toward changes in the proportion of various mineral substances in other diseases, but we do not believe they are sufficiently striking to be significant

# EPHEDRINE

## A CLINICAL STUDY

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Since the isolation of pure ephedrine by Nagai in 1887,<sup>1</sup> several clinical observations have been made with regard to its mydriatic action. Thus Miura<sup>2</sup> in the same year reported that a 6 to 7 per cent solution of ephedrine hydrochloride produces mydriasis in most people in from forty to sixty minutes. He observed that the use of a 10 per cent solution in eighteen patients did not cause a maximal dilatation of the pupils but produced sufficient dilatation for the visualization of the retina. During dilatation, the light reflex is retained, and the accommodation is not paralyzed. There is no increase in intra-ocular pressure, no irritation or inflammation after its instillation and no ill effects after prolonged use. One patient receiving three treatments daily for fifteen days showed no pathologic changes. The duration of mydriasis varies from five to twenty hours. Children and aged people are more susceptible than young adults. The diseased iris does not seem to respond well. De Vriese<sup>3</sup> published identical results in 1889. In 1895, Groenouw<sup>4</sup> reported 100 cases he studied in which the following mixture had been used: ephedrine hydrochloride, 1 Gm., homatropine hydrochloride, 0.1 Gm., water, 10 cc. The mydriasis with this combination begins in eight and one-half minutes, reaches its maximum in thirty-four minutes, and lasts for from four to six hours. The accommodation is not interfered with by this solution. In strong light the pupil contracts to 5.6 mm. in diameter, a size sufficient for ophthalmoscopic examination. Ephedrine at that time cost 9 marks a gram. Groenouw's

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1 Nagai, N. *Ephedra vulgaris* Rich var *helvetica* Hook et Thomp., *Pharm Ztschr* **32** 700, 1887, Ueber die Untersuchungen einer Base der chinesischen Droge Ma Huang, *Yakugaku Zasshi* (*J Pharmaceut Soc Japan*), 1892, no 120, p 901 (original in Japanese).

2 Miura, K. Vorläufige Mitteilung über Ephedrin, ein neues Mydriaticum. *Berl klin Wchnschr* **24** 707, 1887.

3 De Vriese, A. L'éphédrine et la pseudoéphédrine. Nouveaux mydriatiques, *Ann d'ocul* **101**:182, 1889.

4 Groenouw. Ephedrin-Homatropinlösung, ein Mydriaticum von rasch vorübergehender Wirkung, *Deutsche med Wchnschr* **21** 161, 1895.

work was reviewed by Sukei<sup>5</sup> in this country. Favorable results with the foregoing mixture were also reported by Stephenson<sup>6</sup> after its use in twenty patients. All of these workers advocate its use in the exploration of the fundus on account of the rapid action, absence of cycloplegia, short duration of mydriasis and harmlessness. Aside from its original high cost, it is not clear why ephedrine has not become a popular mydriatic drug. Nagai<sup>7</sup> patented his synthetic ephedrine in England, in Canada and in the United States as a mydriatic drug.

Following the isolation and systematic study of ephedrine by Chen and Schmidt,<sup>8</sup> clinical investigations have led in different directions depending on its similar but more prolonged action than epinephrine hydrochloride. One of the important properties of ephedrine as discovered by Cook, is its constricting power on the congested nasal mucosa when applied locally. Fetterolf and Sponsler<sup>9</sup> following Cook's suggestion, found in seventeen patients that a 5 per cent solution of ephedrine sulphate shrinks the turbinates. Contraction begins in from a few seconds to one minute, reaches its maximum in two and one-third minutes, and lasts for three hours and seventeen minutes. There is no nasal irritation, as contrasted with epinephrine used locally. Dunlap<sup>10</sup> obtained encouraging results with the same concentration in a number of cases of acute, subacute and vasomotor rhinitis. Fahr,<sup>11</sup> using a 1 per cent solution, succeeded in relieving headache caused by sinusitis.

Another characteristic of ephedrine is its ability to relieve asthmatic attacks, partially or completely, when taken by mouth. Leopold and Miller<sup>12</sup> treated thirty-six patients, twenty-six of whom showed improvement (72 per cent). Thomas,<sup>13</sup> MacDermot,<sup>14</sup> and Pollak and Robitschek<sup>15</sup> claimed to have obtained the same beneficial results. In

5 Sukei, G. F. Ephedrine-Homatropine, the New Mydriatic, New York M J **61** 714, 1895.

6 Stephenson, S. Some Remarks upon a New Mydriatic (Ephedrine Hydrochloride), Lancet **2** 24, 1898. (Several other references on the subject are mentioned.)

7 Nagai, N. Methylmydriatin Brit Pat no 120936 (1918), Can Pat no 203390 (1920) U S Pat no 1356877 (1921).

8 Chen, K. K., and Schmidt, C. F. The Action of Ephedrine, the Active Principle of the Chinese Drug Ma Huang, J Pharm Exper Ther **24** 339 (Dec) 1924.

9 Fetterolf, G., and Sponsler, M. B. Ephedrin Sulphate, the Alkaloid of Ma Huang Arch Otolaryng **2** 132 (Aug) 1925.

10 Dunlap, A. M. Private communication under date of Jan 12, 1926.

11 Fahr, G. Private communication under date of March 31, 1926.

12 Miller, T. G. Ephedrin Its Use in the Treatment of Vascular Hypotension and Bronchial Asthma, Ann Clin Med **4** 713 (March) 1926.

13 Thomas, W. S. Ephedrin in Asthma, Am J M Sc **171** 719 (May) 1926.

14 MacDermot, H. E. The Use of Ephedrine in Bronchial Asthma, Canad M A J **16** 422 (April) 1926.

15 Pollak, L., and Robitschek, W. Ueber die therapeutische Verwendbarkeit des Ephedrins in der inneren Medizin, Wien klin Wchnschr **39** 753 (June 24) 1926.

accordance with the same principle, Gaarde and Maytum<sup>16</sup> treated twenty-four patients who had ragweed hay-fever, and recorded complete relief in one-half

The purpose of the present investigation was (a) to learn the objective and subjective effects after the internal administration of ephedrine, (b) to make an ophthalmologic study with ephedrine and (c) to ascertain the results of treatment of bronchial asthma with ephedrine. The drug used was in the form either of sulphate or of hydrochloride, made in 1924 under the supervision of one of us (K. K. C.). As a rule, no distinction is made between sulphate and hydrochloride, although theoretically the hydrochloride (containing 81.9 per cent of ephedrine) may be slightly more powerful than the sulphate (containing 77.1 per cent of ephedrine).

#### OBJECTIVE AND SUBJECTIVE EFFECTS OF EPHEDRINE

In order to determine the effects of ephedrine given internally, forty-one patients who were willing to cooperate with us were selected. Twenty-seven of them were males, and fourteen females. The ages varied from 10 years to 71. The majority were young adults. The patients in cases 1 to 5 were Chinese, in case 41 a negress, the remainder were Caucasians. All persons with heart disease, except two (cases 24 and 25), were eliminated from this series. Several asthmatic patients were studied during their attacks, others were free from attacks. Most of these patients were confined to bed for some time, although a few were required to stay in bed only during the period of observation. The drug, dispensed in capsules for oral administration unless otherwise stated, was not given until several blood pressure readings, taken in a recumbent position, were about constant and agreed approximately with those of preceding days. The dosage of ephedrine was variable, in many cases it was large in order to establish the maximal therapeutic dose and to determine tolerance by eliciting the mild toxic symptoms. After the drug was given, the blood pressure was measured and the pulse rate counted at ten or fifteen minute intervals during the first hour, and one-half to one hourly intervals thereafter. Only those subjective symptoms volunteered by the patient were recorded. The results of our fifty-eight observations on forty-one patients after a single dose had been taken are summarized in table 1 and further condensed in table 2.

It should be noted that ephedrine, when given by mouth or injected intramuscularly, with few exceptions, uniformly raises blood pressure. The onset of the rise of the systolic pressure after oral administration of the drug varies considerably, from fifteen to one hundred and twenty minutes, the average being thirty-seven and one-half minutes. The

<sup>16</sup> Gaarde, F. W. and Maytum, C. K. The Treatment of Hay-Fever with Ephedrine. *Am. J. M. Sc.* **172**: 588 (Oct.) 1926.

TABLE 1—The Objective and Subjective Effects after Oral Administration of Ephedrine (Single Dose)

			Objective Effects									
			Arterial Blood Pressure			Pulse, Maximal Change per Minute	Other Signs	Subjective Effects				
Case	Age	Sex	Primary Diagnosis	Ephedrine in Form of	Dose in Mg				Systolic Maximal Change in Mm Hg	Diastolic Maximal Change in Mm Hg	Duration of Change in Hours	
1	30	♂	Addison's disease	Hydrochloride	200	+45	+22	22+	-10			
2	34	♂	Asthma	Hydrochloride	100†	+38	+22	12+	-18			
3	60	♂	Asthma	Hydrochloride	80†	+70	+24	5½+				
4	30	♂	Asthma	Sulphate	160†	+104	+30	7½+	-26			Complete relief of an attack
5	26	♂	Asthma	Hydrochloride	60†	+12	+8	2+	+12			Gradual relief of dyspnea
6	14	♀	Asthma	Sulphate	80†	+17	+14	3	+20			Relief of dyspnea
7	39	♀	Asthma	Sulphate	50	+16	0	4¼	+24			
				Sulphate	100	+50	+34	4¾	-56			Tremor of hands
				Sulphate	100	+52	+26		-20			
8	58	♂	Asthma	Sulphate	150	+14	+10	4+	-8			Relief of dyspnea, palpitation
				Sulphate	200	+26	+10	5	+16			Tremor of hands
				Sulphate	200	+18	+11	4+	-12			
9	68	♂	Asthma	Sulphate	150	+14	+12	3+	-12			Relief of dyspnea
				Sulphate	100	+22	+10	3+	+20			
				Sulphate	200	+12	+6	4	+10			
10	50	♂		Sulphate	100	+52	+10	3¼+	+10			
11	70	♂	Hypothyroidism	Sulphate	150	+8	+2	3+	-1			Relief of dyspnea
			Asthma	Sulphate	150	+50	+11	7+	+16			
12	61	♂	Anthracosis	Sulphate	150	{+6}	-12	3	+1			Partial relief of dyspnea
13	58	♂	Asthma	Sulphate	100	{-10}	+8		+16			
				Sulphate	200	{-12}	+8	3	+12			
				Sulphate	100	{+10}	+17	4+	+22			
14	40	♂	Asthma	Sulphate	100	+34	+16	4+	+14			Relief of dyspnea
				Sulphate	100	+42	+14	4+	+8			
				Sulphate	100	+24	+10	4+	+12			
				Sulphate	100	+22	+18	3+	+8			
				Sulphate	100	+12	+2	3+	-22			
				Sulphate	100	+10	+4	3+	-2			

[illegible]

TABLE 1—The Objective and Subjective Effects after Oral Administration of Ephedrine (Single dose)—Continued

Case	Age	Sex*	Primary Diagnosis	Ephedrine in Form of	Dose in Mg	Arterial Blood Pressure				Objective Effects		Other Signs	Subjective Effects
						Systolic Maximal Change in Mm Hg	Diastolic Maximal Change in Mm Hg	Dura- tion of Change in Hours	Pulse, Maximal Change per Minute				
28	10	♂	Pulmonary tuberculosis	Hydro- chloride	150	-6	-28	3	+24				Tired feeling
29	71	♂	Carcinoma of prostate	Hydro- chloride	300	± 8	{+10} {-12}	3	-8				
30	23	♂	Myosarcoma of hand	Hydro- chloride	150	+6	+8						Insomnia after repeated use
31	78	♂	Hypertrophic irthritis	Hydro- chloride	150†	+10	+10	5+	+16		Electrocardiogram essentially nega- tive		
32	37	♀	Pellagra	Hydro- chloride	150	+46	+10	4+	+24		Extreme diaphoresis	Tremor	Tremor of hands, sweating
33	36	♀	Arthritis deformans	Hydro- chloride	150	+10	+4	3+	+16		Extreme diaphoresis, tremor		Tremor of hands, sweating, chilly feeling, drowsy Weakness, sweating
34	20	♀	Tuberculous peritonitis	Hydro- chloride	150	-2	-10	2	0				
35	33	♀	Syphilis	Sulphate	150	+44	+16	5	{+8} {-12}		Diaphoresis		Feeling of warmth, sweating, palpitation
36	22	♀	Pleural effusion	Hydro- chloride	150	+26	{-4} {+2}	8¼	-18			Palpitation	
37	72	♀	Arthritis deformans	Sulphate	150	+46	+16	7	-6		Diaphoresis		Sweating, headache, nausea, vomiting
38	45	♀	Osteomalacia	Hydro- chloride	150	+18	+10	7	+16		Tremor		Palpitation, feeling of warmth, tremor, vomiting
39	15	♂	Pulmonary tuberculosis	Hydro- chloride	150	+28	+16	6½+	+16				Feeling of warmth, vomiting
40	17	♀	Upper respiratory infection	Hydro- chloride	100	+34	{-4} {+8}	4+	+40			Palpitation	
41	26	♀	Ischio rectal abscess	Sulphate	150	{+2} {-8}	-6	6	+24		Restlessness		Weakness, nervousness, chill- iness, sweating

\* In this column, ♂ indicates male, ♀, female

† Injected intramuscularly

maximum rise occurs in one hour and forty minutes, the shortest time in which this is attained is one-half hour and the longest six hours. The pressure begins to fall in three hours and fifteen minutes, the shortest time in which this occurs is one hour and the longest seven. The duration of the rise of blood pressure in our series was not determined exactly, because it was inconvenient to follow the changes in pressure until the patient had completely recovered, it was especially inconvenient to make these determinations at night. The average duration is approximately five hours and nine minutes. After intramuscular injection, the rise of systolic pressure frequently begins within ten minutes. As shown in our limited number of observations the pressure continues to rise about as long as when the drug is given by mouth.

TABLE 2—*Summary of Table 1*

	Dose of Ephedrine in Mg			
	50-80	100	150 (Incl 160)	200-400
Number of observations	4	15	20	10
Average rise of systolic blood pressure in mm. Hg	29	30	28	27
Number of observations in which toxic symptoms occurred	0	4	14	11
Diaphoresis		1	7	9
Tremor		1	3	3
Extrasystoles		2	1	2
Tonal arrhythmia		2		
Tachycardia				1
Restlessness			1	1
Mydriasis				1
Palpitation		1	4	3
Weakness			3	2
Warmth			4	1
Chilliness		1	3	3
Nausea			1	3
Vomiting			3	
Dizziness				3
Nervousness			1	1
Headache			1	1
Insomnia			1	1
Dyspnea				2
Tired			1	
Drowsy		1	1	
Thirst				1

The maximum rise varies greatly, but the average of all our determinations was 28.5 millimeters of mercury. Increase in dosage does not seem to increase the rise greatly, although in the group of four smaller doses (50 to 80 mg.) case 2 is more of an exception than a rule, which makes its average higher than it really should be. Occasionally the systolic pressure falls following a primary rise (cases 12, 29 and 41), or rises following a primary fall (cases 13 and 20), rarely, it simply falls (cases 25, 28 and 34).

The diastolic pressure as a rule is also increased, but the onset of this rise appears to be slower than that of the systolic pressure, the average period required being fifty-five and one-half minutes. The average maximum rise is 12.5 millimeters of mercury. In seven instances (cases 8, 9, 16, 19, 20, 36 and 40) the diastolic pressure fell before it rose, in four

instances (cases 14, 17, 27 and 29) it fell following a primary rise, and in six instances it fell (cases 12, 18, 25, 28, 34 and 41)

The pulse rate may be increased or decreased during the rise of blood pressure. The average time in which it changes from the original rate is fifty-four minutes after the oral administration of the drug, the extremes being fifteen minutes as the shortest time and one hundred and twenty minutes as the longest time. It returns to the original rate at about the same time that the systolic blood pressure returns to its own level. In twenty-four persons whose pulse rate was more than 80 a minute, fifteen had an acceleration while nine showed a slowing. Similarly, in nine persons whose pulse rate was 80 or less a minute, in seven the rate was increased and in two decreased. It seems that cardiac stimulation by ephedrine frequently overcomes the vagal tone.

TABLE 3—*Results of Administration of Ephedrine Sulphate in Case 15*

Date	Time	Blood Pressure	Remarks
1/ 6/26	8 45 a m	82-60	Dyspnea and orthopnea
1/ 8/26	10 20 a m	78-64	Râles in the chest
	10 50 a m		Ephedrine therapy begun
	12 10 p m	88-76	
1/ 9/26	8 00 a m	104-72	
1/10/26	9 30 a m	102-78	Comfortable, chest clear
	4 45 p m	98-78	
1/11/26	8 00 a m	80-62	Urine showed albumin and casts
	1 15 p m	82-66	
	4 45 p m		Very tired, râles in chest, urine free from albumin and casts
1/12/26	10 20 a m	104-76	
1/13/26	8 00 a m	86-72	Chest clear
1/14/26	1 10 p m	90-74	Marked improvement
1/15/26	10 15 a m	94-74	
1/16/26	10 00 a m	88-68	Improvement continued
1/17/26	9 30 a m	98-76	Patient lay flat on back, chest clear
1/18/26	8 00 a m	104-80	
1/19/26	8 00 a m	88-66	Ephedrine stopped

Three of our patients who had hypotension (cases 11, 15 and 21)—two with asthma and one without asthma—were given ephedrine at frequent intervals for a considerable length of time, in the hope of elevating their blood pressure and maintaining the higher pressure. The results in two were practically negative. The slight elevation in the third shown in table 3 was probably due to the improvement of his asthmatic condition under ephedrine therapy.

CASE 15—Beginning Jan 8, 1926, at 10 50 a m, T W, aged 38, afflicted with bronchial asthma and arthritis deformans, was given 150 mg of ephedrine sulphate by mouth every three hours, day and night, for the first eight days. The dose thereafter varied.

At the time of discharge, this patient had received a total quantity of more than 11 Gm of ephedrine sulphate. Laboratory reports recorded no additional pathologic conditions caused by the use of the drug. While such massive doses are not to be advocated for general use, this experiment is reported here only to show the low toxicity of the drug.

With regard to the untoward symptoms after the administration of ephedrine, both objectively and subjectively, the dosage is undoubtedly

an important factor. In eleven cases, electrocardiograms were taken at different intervals after the administration of ephedrine. Seven of the patients presented no changes, while four (cases 16, 19, 25 and 26) had extrasystoles of ventricular or auricular origin, these were more numerous in a patient with chronic myocarditis (case 25) in whom the systolic blood pressure fell 30 millimeters of mercury. In case 26 the patient developed a paroxysm of tachycardia (rate 196 a minute), possibly due to overdosage. It lasted for only a few minutes but was alarming. Electrocardiographic records were not taken. On questioning, the patient said that he had had attacks of tachycardia like this previously. In a patient who had auricular fibrillation (case 24) and who was in a critical condition, ephedrine raised arterial blood pressure, lowered venous pressure and stopped the hiccup. The woman died twenty hours following the administration of the drug. Necropsy showed subdiaphragmatic abscess and extensive mesenteric thrombosis constituting the cause of death. It should, however, be borne in mind that the drug should be administered with extreme caution to patients with cardiovascular diseases. The danger of dislodgement of valvular vegetations or thrombi, and of the rupture of sclerotic vessels during the cardiac stimulation and the rise of blood pressure, is too obvious to require comment. Besides, increasing doses of ephedrine may depress the heart, especially in case of marked deficient circulation as already shown in animals by Chen and Meek<sup>17</sup>. The fall of systolic pressure in a few of our patients is probably an indication of this fact.

From table 2 it will be noted that one or more untoward symptoms occurred in eleven of nineteen observations (58 per cent) with a dose of from 200 to 400 mg of ephedrine, in fourteen of twenty observations (70 per cent), with a dose of 150 mg, in four of fifteen observations (27 per cent), with a dose of 100 mg, and none in four observations with a dose of from 50 to 80 mg. Objectively, the common signs are diaphoresis, tremor, extrasystoles and tonal arrhythmia, while those of less frequent or rare occurrence are tachycardia, restlessness, and mydriasis. Subjectively, the common symptoms are palpitation, trembling, weakness, sweating, feeling of warmth, chilly sensation, nausea, vomiting and dizziness, while those of less frequent or rare occurrence are nervousness, headache, insomnia, dyspnea, a tired feeling, thirst and drowsiness. Tonal arrhythmia, extrasystoles and palpitation may appear as soon as the systolic blood pressure begins to rise, and become more pronounced as the blood pressure reaches the maximum. Tremor, perspiration, feeling of warmth, chilliness, gastric distress and other symptoms usually do not occur until the blood pressure attains the highest level. Frequently subjective symptoms are aggravated by

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17 Chen, K. K., and Meek, W. J. Further Studies of the Effect of Ephedrine on the Circulation, *J. Pharm. Exper. Therap.* **28**: 31 (July) 1926.

meals (our patients were allowed to sit up to eat their meals) All the untoward symptoms begin to abate shortly after the blood pressure begins to fall, and to disappear as the latter returns to its normal level In a few instances, the patients say that they are tired or weak after all the symptoms have disappeared This sensation may persist for a few hours

It is interesting to note that perspiration caused by the use of ma huang, firmly believed by the Chinese and described by Li Shih-Cheng in his *Pentsao Kang Mu*,<sup>18</sup> although not experimentally proved in animals, has been clinically confirmed in a number of our cases

Our other laboratory reports are not of sufficient value to be mentioned here It may well be pointed out that Miller<sup>19</sup> and Rowntree and Brown<sup>20</sup> have demonstrated the increase of metabolic rate after the administration of ephedrine, and Starr<sup>21</sup> has shown a transient albuminuria in certain cases which is due to renal vasoconstriction and not to intrinsic injury of the kidney

#### AN OPHTHALMOLOGIC STUDY OF EPHEDRINE

The mydriatic action of the following six aqueous solutions was studied and compared in men

(a)	Ephedrine sulphate	10	per cent
(b)	{ Ephedrine sulphate	10	per cent
	{ Homatropine hydrobromide	0.1	per cent
(c)	Homatropine hydrobromide	0.1	per cent
(d)	Homatropine hydrobromide	2	per cent
(e)	{ Ephedrine sulphate	10	per cent
	{ Atropine sulphate	0.1	per cent
(f)	Atropine sulphate	0.1	per cent

These solutions were all freshly and quantitatively made A series of sixty-three patients who had normal eyes was selected, that is, patients who had no ocular inflammatory diseases The majority of them remained in bed during the period of observation In each case, 1 or 2 drops of one of the solutions was instilled into one conjunctival sac The patient was requested to close the eyes for from 5 to 10 minutes after application The transverse diameter of the pupil was measured by a serrated rule as shown in figure 1 every ten or fifteen minutes during the first hour, and at hourly intervals thereafter When the diameter of the

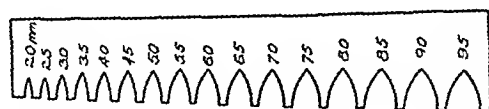
18 Li, Shih-cheng Ma Huang, *Pentsao Kang Mu*, 1596, chap 15 (in Chinese)

19 Miller, T G A Consideration of the Clinical Value of Ephedrine, *Am J Med Sc* **170** 157 (Aug) 1925

20 Rowntree, L G, and Brown, G E Ephedrin Therapy in Addison's Disease, *Endocrinology*, **10** 301 (May-June) 1926

21 Starr, I The Production of Albuminuria by Renal Vasoconstriction in Animals and in Man, *J Exper Med* **43** 31 (Jan) 1926

pupil was measured, the patient was directed to look at a fixed distant object, otherwise a hippus may develop. The light reflex was tested with an ordinary flashlight with a two cell battery held in front of the eye at a distance of about 5 cm. In several cases, the near point was tested with Jaeger's test type 2 on a Prince's rule for the condition of accommodation. When a solution was studied alone, the entire duration of mydriasis was recorded as soon as the pupil of the treated eye



A serrated rule for measuring the transverse diameter of the pupil

equaled that of the control eye. When a solution was compared with another in the same subject, the duration of mydriasis of the weaker one was determined when the pupil under the flashlight returned to the same size as before instillation, while that of the stronger one was determined when the pupil equaled that of the fellow eye. The results are compared in table 4.

TABLE 4—*Comparison of Mydriasis with Different Solutions*

Solution	Time Required for Maximal Dilatation of Pupil After an Instillation	Mean Value* of Maximal Transverse Diameter of Pupil in Diffuse Daylight	Average Duration of Mydriasis
(a)	30-60 minutes	7.5 mm	6¼ hours
(b)	30-40 minutes	8.0 mm	12 hours
(c)	60 minutes	6.8 mm	8¼ hours
(d)	30-60 minutes	7.8 mm	50½ hours
(e)	30-60 minutes	8.0 mm	32¼ hours
(f)	40-60 minutes	7.8 mm	129½ hours

\* Mean value is the average of the two or three central figures of the data arranged numerically.

With a 10 per cent solution of ephedrine sulphate (a), twenty-two observations were made. The solution is only slightly irritating. The patient may complain of smarting or burning and a little lacrimation, all of which last for a few seconds. When the solution came in contact with the swollen turbinates in a few patients through the lacrimal duct, a relief from the obstruction was felt. If it gains access to the mouth, a bitter taste is experienced. No conjunctival injection has been seen. Mydriasis definitely begins, in the majority of cases, within from fifteen to thirty minutes, in a few, within ten minutes. The maximum dilatation is attained between from thirty to sixty minutes, in seven it occurred within thirty minutes. The size of the pupil during maximum mydriasis depends on the individual and on the weather. In ordinary diffuse light, with no sunlight penetrating the room and with the patient not too close to the window, the diameter after ephedrine varies from

6.5 to 9.5 mm Under the flashlight, it contracts to 5.5 to 7 mm, whereas the pupil of untreated persons measures from 2 to 4 mm With the ordinary May ophthalmoscope, the pupil contracts to only from 6.5 to 8 mm, and the retina can then be examined satisfactorily In no case is there any interference with accommodation The mydriasis begins to fade away from one to three hours after the instillation and disappears completely in from three to nine hours, the average being approximately six and one-fourth hours Only in exceptional cases does ephedrine fail to produce mydriasis

By the addition of 0.1 per cent homatropine hydrobromide to a 10 per cent ephedrine solution (*b*), mydriasis seems to have an earlier onset In the majority of twenty-four cases observed, mydriasis began within from ten to fifteen minutes and reached the maximum dilatation within from thirty to forty minutes Compared with effects of a 10 per cent ephedrine solution alone, the mixture as a rule produces a greater dilatation by from 0.5 to 1 mm, so that a better view of the retina is obtained In four instances the dilatation following the use of the two solutions was equal, and in four other instances the pupil after the administration of ephedrine was larger than after the use of the mixture Close reading is possible under the ephedrine-homatropine combination, and the light reflex present but sluggish The mydriasis begins to wear off in from two to four hours, and disappears completely in from four to twenty-two and one-fourth hours (average twelve hours) after the time of instillation

A comparative study of this mixture with 0.1 per cent homatropine solution (*c*) is also important in order to determine any summation or potentiation between ephedrine and homatropine Groenouw did not control his series with this solution In our five observations, it was found that homatropine of that concentration also produces a mydriasis which begins in from twenty to forty minutes, and lasts from five to seventeen and one-half hours (average eight and three-fourth hours) after the application of this solution The pupil during maximum dilatation measures from 0.5 to 2 mm less in diameter than it does following the use of ephedrine-homatropine mixture, which sometimes permits a good view of the eyegrounds There is no cycloplegia or absence of light reflex The combined action of ephedrine and homatropine in the concentrations given here is probably a case of "deficient summation" <sup>22</sup>

A 2 per cent solution of homatropine hydrobromide (*d*), the common form of eye drop, in our nine observations showed that the mydriasis begins almost within ten minutes, reaches its maximum in from thirty to sixty minutes and lasts for from twenty-four to one hundred and four and one-half hours Patients invariably complain of blurring vision The light reflex is abolished for an hour or longer

It is clear from the foregoing data that ephedrine, or ephedrine with the addition of homatropine as shown in the prescribed formulas, can serve as a convenient, harmless and efficient mydriatic for the ophthalmoscopic examination of the fundus. The 10 per cent ephedrine alone should be especially useful in those glaucomatous cases in which atropine or homatropine is contraindicated. It does not cause drying with resultant desquamation of the corneal epithelium, as is frequently seen after the use of cocaine. The ephedrine solution is stable to light, air, heat and standing, while the ephedrine-homatropine mixture may have a black sediment in two weeks, probably denoting the deterioration of homatropine. In our medical wards, the ephedrine-homatropine combination is used in young adults and children, but ephedrine alone in elderly patients, for the routine study of the eyegrounds by the interns.

TABLE 5—*Comparison of Mydriasis between Ephedrine-Atropine and Atropine Solutions with Reference to Speed and Size of Pupil\**

Time After Instillation		Oculus Dexter Transverse Diameter of Pupil in Mm		Oculus Sinister Transverse Diameter of Pupil in Mm	
Hours	Minutes	Daylight	Bright Light	Daylight	Bright Light
	0	5	4	5	4
		Solution (e), 2 drops locally		Solution (f), 2 drops locally	
	10	6	4	5	3.5
	20	7.5	7	6	6
	30	8	7.5	6.5	6.5
	40	8.5	8.5	7	7
	50	8.5	8.5	7.5	7.5
	60	8	8	7	7
2		8	8	7	7
4		8	8	7	7
7		8	7	7	7
8		8	6.5	7	7
10		7.7	5.5	7	7
12		7	6	7	6
24	25	6.5	4	7	6
35	25	5	4	6.5	6
95	17	5		6	
152	30	5		5	

\* A man, aged 59, had a condition primarily diagnosed as hyperthyroidism.

The combination of a 10 per cent ephedrine solution with 0.1 per cent atropine sulphate (e) presents an interesting phenomenon. This mixture produces a mydriasis, beginning in from five to thirty minutes, frequently within ten minutes, reaching the maximum in from thirty to sixty minutes (average fifty-four minutes), and lasting from eleven to ninety-six hours (average thirty-two and three-fourths hours) after instillation. There is brief paresis of accommodation and disappearance of light reflex. The pupil during the maximum mydriasis is larger, by from 0.5 to 2 mm, than that after the use of a 10 per cent ephedrine solution alone and also frequently larger than that after the use of 2 per cent homatropine solution. Dilatation of pupils with this mixture is probably maximal. The interesting phase occurs when the mixture is compared with 0.1 per cent atropine solution (f). Tables 5 and 6 giving the results in two of our twenty-four observations may be taken as typical examples.

It will be seen that the mydriasis, after the administration of 0.1 per cent atropine solution, is slower in its onset and development, but much more persistent than that after ephedrine-atropine combination. There is also more extensive paresis, and slower return of accommodation. The modus operandi of this phenomenon is not clear at present. Apparently there is synergy between ephedrine and atropine in the speed and size of pupillary dilatation, but antagonism with reference to cycloplegia and duration of mydriasis. It is hoped by further study that practical use may be made of this phenomenon in refraction by finding a suitable concentration of atropine, possibly homatropine also, sufficient to produce complete cycloplegia with the addition of ephedrine to shorten the duration of cycloplegia and mydriasis.

TABLE 6—*Comparison of Mydriasis between Ephedrine-Atropine and Atropine Solutions with Reference to Duration and Accommodation.\**

Time After Instillation		Oculus Dexter			Oculus Sinister		
		Transverse Diameter of Pupil in Mm		Near Point in Cm	Transverse Diameter of Pupil in Mm		Near Point in Cm
		Daylight	Bright Light		Daylight	Bright Light	
Hours	Minutes						
	0	5.5	3	12	5.5	3	12
		Solution (e), 1 drop every 7 minutes for 7 doses			Solution (f), 1 drop every 7 minutes for 7 doses		
1		9.5	9.5	14	9	9	∞
2		9.5	9.5	31	9	9	∞
3		9.5	9.5	∞	8	8	∞
5		9.5	9.5	∞	8	8	∞
16	38	7.5	6.5	30	8	8	∞
21	55	6.5	6.5	16.5	7.5	7.5	∞
25	15	5.5	4	15.7	7.5	7.5	∞
40	55	6	4	14.5	8	7	28
44	42	5.5	3	12	6.5	5.5	23
64	40	4	3	14	6.5	5.5	17
69	45	3.5	3	11.5	5.5	5	14

\* A woman aged 32 had a condition primarily diagnosed as arthritis deformans.

#### TREATMENT OF BRONCHIAL ASTHMA WITH EPHEDRINE

In order to test the efficacy of ephedrine in the treatment of bronchial asthma, twenty-five patients were studied. This group was an unselected one, in which the duration of the condition ranged from weeks to almost a half century, the frequency of the attacks, from once a year to a constant condition, and the duration of the attacks from a number of hours to years.

The drug was given by mouth, unless otherwise stated, for the purpose of controlling the paroxysms of asthma, except in two cases in which it was used as a prophylactic. The dose employed by us was from 50 to 100 mg, but in a few cases it was larger, as mentioned in the foregoing, in order to establish maximum therapeutic dose and also the tolerance as manifested by mild toxic symptoms. The interval between doses was arbitrary depending on the tolerance of the patient and the severity of the condition, but in no case was the drug given more

frequently than every two hours. The duration of ephedrine therapy varied considerably, depending on the condition and indications.

In recording the progress in these cases, a conservative attitude was taken. The psychic factor of the patients was carefully considered. Only reasonable and convincing statements were accepted. In several cases, hypodermic injections of epinephrine were used, but they were always withheld as long as possible in order to give ephedrine a fair trial. If the administration of ephedrine was obviously useless in the control of attacks, the patient was said to be unaffected by this therapy.

It must be confessed that our experience with ephedrine in the treatment of asthma at present is limited. There are a few cases, however, in which the beneficial effects are unmistakable. The results of our cases are summarized in table 7. In this group the paroxysms of bronchial asthma were controlled in nine instances (36 per cent), and eight patients (32 per cent) were improved by ephedrine, so that seventeen of the total twenty-five may be classed as benefited by the use of ephedrine. The remaining number showed no conclusive or negative results. No apparent relation exists between the factors of duration and severity, and the response to ephedrine, nor is there apparent relationship between the specific allergic basis (in the few cases where such was determined) and the reaction to ephedrine. Different persons apparently have different susceptibility toward the drug. Thus one patient (case 15) was always comfortable after doses of from 150 to 200 mg. given at frequent intervals, while another (case 49) complained of a severe headache which was just as bad as, if not worse than, the asthmatic attack, even though ephedrine gave her relief on several occasions. This patient had similar but more pronounced discomfort with epinephrine. In several instances, it appears that epinephrine controls severe attacks when ephedrine fails. Such a difference of action is to be expected from the results of Chen and Schmidt's conclusion in animals that epinephrine is a stronger bronchodilator. Cases 52 and 53 seem to indicate that the drug can be used as a prophylactic against the occurrence of expected attacks. The advantages of ephedrine as a drug in those cases in which it produces definite improvement are obvious: effectiveness of administration by mouth, relatively low toxicity and the fact that it can be used as a substitute for epinephrine at least in mild and moderate attacks.

The following case occurring in a physician, because of the accuracy of the report, is described here as a type of the subjective reactions, although the response has not been as spectacular nor the relief as complete as in others of this group.

CASE 52—W. C. J., aged 41, a white man, unmarried, a physician, complained of asthma of thirteen years' duration. Fourteen years ago, a marked nasal obstruction with the loss of smell and taste senses, occurred. Following a nasal operation there was temporary relief, but coryza eventually led to a chronic bronchitis with

TABLE 7—The Results of Ephedrine Therapy in the Treatment of Bronchial Asthma

Case	Sex*	Age	Duration	Allergy	Attacks		Ephedrine		Results	
					Frequency	Duration	Dose, Mg	Interval	Objective	Subjective
3	♂	60	10 years	None	Irregular	?	Intramuscularly 160	Single dose	Fewer rales, no dyspnea	Complete relief
4	♂	30	7 8 years	None	Night, winter (4 5 a year)	4 5 days, late 10 days	Intramuscularly 20 60 60 80	Single doses	Fewer rales, no dyspnea	Complete relief
5	♂	26	6 months (?)	None	Third attack in 6 months	12 hours +	Intramuscularly 40 to 80	Single doses	Fewer rales, more comfortable	Complete relief
6	♀	14	9 years	Egg white?, egg yolk?	Twice a year	Present attack 8 months	50	Single dose	Inconclusive since no attacks in hospital	Better
7	♀	39	10 years	None	Continuous		100	Daily	Fewer rales, less dyspnea	Complete relief
8	♂	53	15 years	None	2 to 7 times a year	Up to con- tinuous	100 to 150 50 75 100	Irregularly thereafter Single doses Three times a day Three times a day Three times a day	No rales, no dyspnea	Complete relief
9	♂	63	6 years	?	Irregular	Present attack 5-6 weeks	50	Three times a day	No rales, no dyspnea	Complete relief
11	♂	70	5 years	None	Irregular	Hours	150 50	Single dose Three times a day	Fewer rales, less dyspnea	Probable marked improvement
13	♂	18	4½ years	?	Variable	Present 5 mo., in main nocturnal	100	Single	Unimproved	No change
14	♂	40	2 weeks	Bacterial?	First (?)	?	150	Three times a day	Unimproved	No change
15	♂	33	4½ years	None	Nightly	Hours	200 150 150 100 1-400 100	When necessary Every 3 hours Every 6 hours Every 3 hours Single doses When necessary	Fewer rales, less dyspnea	Marked im- provement
12	♂	67	10 months	None	Continuous		150	Single dose	Unimproved	No change
43	♀	50	13 years	None	Winter and respiratory infection	Variable	50 100	Three times a day Three times a day	Less dyspnea Fewer rales	Doubtful

44	♀	49	5 years	?	Nightly	Hours to a day	100	Twice a day	4 days	No rales, no dyspnea	Complete relief
45	♂	65	2 years	?	Present attack since 6 weeks ago		100	Twice a day	13 days	Less cyanosis, fewer rales, less dyspnea	Less cough, only nocturnal dyspnea
46	♂	48	2½ years	Bacterial?	Nightly	Hours	150	Every 4 hours	21 days	No rales, no dyspnea	Complete relief
47	♀	57	9 years	None	Summer	10 to 35 days	100	Every night	2 days		
48	♂	51	15 years	?	Irregular	Irregular	50	Every night	6 days		
49	♀	39	Since adolescence	Wheat proteose grape	Summer, as rule	Weeks	50	Twice a day	7 days		
50	♂	59	49 years	None	Irregular, usually fall	1 to 2 days now	25	Twice a day	9 days		
51	♀	52	4 months	Tomato?, potato?	Nightly, irregular	4 months	100	Twice a day	10 days		
52	♂	41	13 years	Bacterial?	Few days to months	1 to 4 hours, 3 to 5 days succeeding dyspnea	100	Twice a day	1 day		
53	♀	28	20 years?	Succeeded hay-fever	Weekly for year	Hours to days	50-150	When necessary to meet attacks or as prophylaxis	7 days	Effective in slight and moderate attacks and in prophylaxis	
54	♂	38	2 years	None	2 to 10 a year	4 days	25-50	As prophylaxis	1 day	Effective in prophylaxis	
55	♂	37	28 years	None	Tall, irregular	Variable	Intramuscularly 150	Single dose	20	No dyspnea	Complete relief
							50	Twice a day	2	No control from smaller dose, even supported by epinephrine, marked relief, subjective and objective, from larger dose	

\* In this column, ♂ indicates male, ♀, female

nightly paroxysms of coughing. Dyspnea occurred and became more and more severe. Coincidentally an ethmoiditis developed, and all the sinuses became involved. With the exception of occasional periods of freedom from asthma varying from a few days to several months, the paroxysms recurred practically daily. In severity they varied from slight wheeziness to attacks accompanied by profound dyspnea. As a rule, at night the attacks continued for from one to four hours. Coryzal attacks as a rule were succeeded by acute bronchitis, and bronchial casts were produced. With such acute respiratory infections there was intense and almost continuous dyspnea for from three to five days. No evidence, either clinical or laboratory, of an allergy was found, and it was concluded that the asthma was secondary to sinusitis and bacterial infection. Sodium iodide was given in doses of from 5 to 20 grains (0.3 to 1.3 Gm.) a day. When the patient has had severe attacks, he has been given subcutaneous injections of epinephrine hydrochloride in from 0.5 to 0.75 cc. doses, until a disturbing degree of tolerance has resulted. Moderate doses of epinephrine have been ineffective in controlling the attacks. The usual inhalations of stramonium, belladonna and potassium nitrate have proved useful in controlling the more severe attacks. Acetylsalicylic acid has apparently decreased the intensity of the dyspnea, when an acute respiratory infection has initiated the attack. Morphine, used only twice, has had but a moderate effect. At times bacterial vaccines, both autogenous and stock, have seemed to be beneficial, but the results have been inconsistent.

Over a period of six months ephedrine sulphate has been used in doses of from 50 to 150 mg., administered in capsules by mouth. The patient has thus described the action of the drug: "The effect of the drug is first noticed about one-half hour after administration and consists in a sudden increase in the force of the heart beat, which becomes very noticeable to the patient. The forcible heart action is marked for two or three hours, and may be noticed to a lesser degree for two or three hours more. Soon after the effect on the heart is first noticed, there is a gradual relief of the dyspnea. The relief is much less prompt and less marked than after administration of epinephrine hydrochloride. Complete relief has been obtained with ephedrine only in attacks of slight or moderate intensity. In severe attacks the effect of ephedrine has been slight, and on several such occasions no perceptible relief has been obtained.

"During the height of the effect of the drug there is an apparent general stimulating action, with sensations of increased muscular strength and energy—more than can be accounted for by relief of the dyspnea. As the effect of ephedrine wears off, the period of stimulation is followed by one of weariness and relaxation—often with a desire to sleep. When there has been a regular recurrence of asthmatic paroxysms every night, a dose of 50 mg. of ephedrine at bedtime has on several occasions prevented the expected attacks, but this has not been tried for more than a few nights in succession on account of the limited quantity of the drug available."

#### CONCLUSIONS

We have concluded, from fifty-eight observations on forty-one patients, that ephedrine in the form of sulphate or hydrochloride, when given by mouth (in six observations the drug being injected intramuscularly), in varying doses, causes an average rise of systolic blood pressure of 28.5 millimeters of mercury. The average duration of this rise is approximately five hours and nine minutes. The diastolic pressure, as a rule, is also elevated. The pulse is more frequently accelerated than it is slowed.

The therapeutic dose advocated for oral administration in adults is from 60 to 90 mg., or from 1 to 1½ grains.

The common untoward symptoms from larger doses, objectively and subjectively, are diaphoresis, tremor, extrasystoles, tonal arrhythmia, palpitation, weakness, a feeling of warmth, chilly sensation, nausea, vomiting and dizziness. Others of less frequent or rare occurrence are tachycardia, restlessness, mydriasis, nervousness, headache, insomnia, dyspnea, tired feeling and drowsiness. The drug should not be used without extreme caution in cases of cardiovascular diseases or markedly deficient circulation.

A 10 per cent solution of ephedrine sulphate, or the same concentration with the addition of 0.1 per cent of homatropine hydrobromide may be used locally as a mydriatic for routine ophthalmoscopic examinations. The former is probably more adaptable in elderly people, while the latter is suitable for adults and children. These solutions produce rapid mydriasis, they do not produce undesirable effects or cycloplegia.

A 10 per cent solution of ephedrine sulphate with the addition of 0.1 per cent atropine sulphate produces an almost maximum dilatation of the pupil with a brief paresis of accommodation and disappearance of the light reflex. The mydriasis effected by 0.1 per cent atropine sulphate alone is slower in its onset and development, but much more persistent than the ephedrine-atropine combination. There is also more extensive paresis and slower return of accommodation. Ephedrine seems to show synergism for atropine in the speed and size of pupillary dilatation, but antagonism to atropine with reference to cycloplegia and duration of mydriasis.

Ephedrine, in a group of twenty-five unselected patients with bronchial asthma, controlled the attacks in nine instances and caused improvement in eight other cases, but showed inconclusive or negative results in the remainder.

Our indebtedness is due to Drs Henry E. Meleny and George A. Harrop for their interest in the study of the Chinese patients at the Peking Union Medical College Hospital, to Dr F. A. Davis for his assistance in the ophthalmologic work, to Dr Edwin D. McKinley for his assistance in the observation of several cases, and to Miss Dorothy Reid for her assistance in electrocardiography.

#### APPENDIX

While this paper was in press, the following articles on ephedrine appeared in German literature:

Hess, F. O. Ueber Ephedrin, *Munchen med. Wchnschr.* **73** 1691 (Oct. 8) 1926.

Kammerer, H., and Dorrer, R. Kurze Mitteilung uber die Wirkung des Ephedrins-Merck auf Asthmarkranke, *Munchen med. Wchnschr.* **73** 1739 (Oct. 15) 1926.

Heller, E. Selbstbeobachtung uber Ephedrin Merck bei Asthma bronchiale, *Die Therapie der Gegenwart* **67** 567 (Dec.) 1926.

Jansen. Ueber Ephedrin, *Klin. Wchnschr.* **5** 2402 (Dec. 17) 1926.

Kreitmaier, H. Die Wirkung von Ephedrin-Merck auf den experimentell erzeugten asthmatischen Anfall, *Klin. Wchnschr.* **5** 2403 (Dec. 17) 1926.

# A COMPARATIVE STUDY OF EPHEDRINE, PSEUDO-EPHEDRINE AND $\beta$ -PHENYL-ETHYLAMINE

WITH REFERENCE TO THEIR EFFECTS ON THE PUPIL  
AND ON THE BLOOD PRESSURE \*

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Previously Dr Meek and I<sup>1</sup> made a comparative study of ephedrine, tyramine and epinephrine, with special reference to the circulation, and made the assertion that the stability of ephedrine to physical and chemical agents, and that its persistence of systemic action when taken by mouth, are chiefly caused by the absence of the hydroxyl group in the benzene ring. A similar opinion is also shared by Kendall of the Mayo Clinic<sup>2</sup>. If, however, this were the only factor, the same would be expected to hold for  $\beta$ -phenyl-ethylamine,  $C_6H_5,CH_2,CH_2,NH_2$ , and an identical effect expected from pseudo-ephedrine, which has the same structural formula but an opposite optical rotation (Dextrorotatory)—both of them being devoid of phenolic hydroxyls. The present study is undertaken to test whether or not this assumption is true by comparing the mydriatic action of these three amines in animals and in man, and their pressor action in dogs and in man.

Before the presentation of the results, it may be helpful to give a brief account of the physiologic studies made by previous workers with  $\beta$ -phenyl-ethylamine and pseudo-ephedrine. The former has been recognized as a sympathomimetic amine by Baizer and Dale<sup>3</sup>. The work of Barbour and Frankel<sup>4</sup> on the heart suggests strongly its resemblance in action to ephedrine, as reported by Chen and Meek<sup>5</sup>. Small doses stimulate, but large doses depress, the mammalian heart. Using

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<sup>1</sup> This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association

1 Chen, K K, and Meek, W J. A Comparative Study of Ephedrine, Tyramine and Epinephrine with Special Reference to the Circulation, *J Pharmacol & Exper Therap* **28** 59, 1926

2 Rowntree, L G, and Brown, G E. Ephedrin Therapy in Addison's Disease, *Endocrinology* **10** 301, 1926

3 Barger, G., and Dale, H H. Chemical Structure and Sympathomimetic Action of Amines, *J Physiol* **41** 19, 1910

4 Barbour, H G, and Frankel, E M. The Action of Phenylethylamin on the Heart, *J Pharmacol Exper Therap* **7** 511, 1915.

5 Chen, K K, and Meek, W J. Further Studies on the Effect of Ephedrine on the Circulation, *J Pharmacol & Exper Therap* **28** 31, 1926

pseudo-ephedrine, DeVriese<sup>6</sup> observed that a 10 to 12 per cent solution when applied locally to the eye of man produces, in from thirty to thirty-five minutes, mydriasis which lasts for from six to nine hours. There are no secondary effects after a single instillation, nor after its prolonged use, and no changes in intra-ocular pressure. Gunsburg<sup>7</sup> in an extensive study on animals and on 120 patients, presented evidence that the mydriasis produced by pseudo-ephedrine is possibly caused by the sympathetic stimulation. Fujii<sup>8</sup> recently made a comparative study of pseudo-ephedrine with ephedrine, he came to the conclusion that pseudo-ephedrine, like ephedrine, stimulates the sympathetic nerve endings, but, unlike ephedrine, acts on smooth muscles in small doses. In all probability, pseudo-ephedrine is a sympathomimetic amine. Fujii's data showed that the mydriasis of the enucleated frog's eye after the administration of ephedrine is greater than that after the administration of pseudo-ephedrine, and that the rise of blood pressure in rabbits following an intravenous injection of ephedrine is higher than after pseudo-ephedrine similarly administered.

#### EXPERIMENTAL WORK

*Relative Effects on the Pupil*—The  $\beta$ -phenyl-ethylamine was synthesized for this experiment by Dr. C. H. Kao according to the method described by Noyes<sup>9</sup> from the reduction of benzyl cyanide by means of metallic sodium in absolute alcohol. Its hydrochloride melts at 216.5 degrees corrected. The pseudo-ephedrine hydrochloride (m.p. 180.5 degrees uncorrected, 182.5 degrees corrected) was purchased from E. Merck, Darmstadt, Germany, and the ephedrine hydrochloride (m.p. 216 degrees corrected) was prepared in 1924 under my supervision.

The solutions of  $\beta$ -phenyl-ethylamine hydrochloride, varying from 1.6 to 10 per cent, are clear and stable but show a slight sedimentation after standing for two months. At the end of this period, however, they are almost as potent when injected into animals as when freshly made. The 20 per cent solution is slightly turbid. The solutions of pseudo-ephedrine hydrochloride behave similarly to those of ephedrine hydrochloride, that is, they are stable to air, light and standing.

When the solutions of  $\beta$ -phenyl-ethylamine hydrochloride, varying from 1.6 to 10 per cent, were instilled into the eyes of rabbits and kittens,

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6 DeVriese, A. L'éphedrine et la pseudoéphedrine, nouveaux mydriatiques, Ann. d'ocul. **101** 182, 1889.

7 Gunsburg, F. Ueber Pseudoephedrin, Virchows Arch. f. path. Anat. **124** 75, 1891.

8 Fujii, M. Ueber die pharmakologischen Wirkungen des Pseudoephedrins und deren Vergleich mit der des Ephedrins, J. Oriental Med. **3** 1, 1925.

9 Noyes, W. A. Organic Chemistry for the Laboratory, ed. 3, Easton, Pa., Chemical Publishing Company, 1916, p. 228.

no mydriasis occurred, nor was there any evidence of dilatation of pupils after the subcutaneous injection of 18 mg per kilogram in rabbits. However, when a large dose of from 200 to 600 mg per kilogram was injected subcutaneously, a dilatation of the pupils was seen in a few minutes. This may not be caused by the specific action of the drug on the pupil, but may be one of the toxic symptoms. In a single case in man, a drop of 20 per cent solution, applied locally, increased the transverse diameter of the pupil by from 1 to 2 mm for two hours. The solution was so irritating, causing conjunctival injection for approximately thirty minutes, that further extensive study was not justified.

For the comparison of mydriasis produced by ephedrine hydrochloride and pseudo-ephedrine hydrochloride, respectively, 10 per cent solutions, freshly and quantitatively made, were used. In

TABLE 1—*Comparison of Mydriasis in Man Caused by a 10 per cent Solution of Ephedrine Hydrochloride and That Caused by a 10 per cent Solution of Pseudo-Ephedrine Hydrochloride*

Initials	Sex*	Age	Maximum Mydriasis of the Eye with Ephedrine in Mm	Maximum Mydriasis of the Fellow Eye with Pseudo ephedrine in Mm
M W	♂	16	7.5	6.0
P O	♂	33	5.5	5.0
C D	♂	21	8.5	8.0
L S	♂	23	8.5	7.5
M H	♂	40	7.5	7.0
E B	♂	25	6.5	4.5
C V	♂	25	9.5	9.0
W P	♂	25	9.0	8.5
E S	♂	9	8.5	8.0
E W	♂	6	9.0	8.5
F S	♂	13	8.0	7.5
R S	♂	11	8.5	8.0
G H	♂	8	9.5	8.5
M L	♂	11	9.5	9.0
Average			8.2	7.5

\* In this column, ♂ indicates male, ♀, female

fourteen persons who presented equal pupils and no ocular inflammatory diseases, 2 drops of ephedrine hydrochloride were instilled into one eye and the same number of drops of pseudo-ephedrine hydrochloride into the other at the same time. The subjects were directed to close their eyes for ten minutes. The transverse diameters of the pupils were measured by a serrated rule at fifteen minute intervals during the first hour, and at one-half to one hourly intervals thereafter until normal size was restored. The results are summarized in table 1.

It will be seen that the average maximum dilatation of the pupil after the instillation of ephedrine hydrochloride is 0.7 mm greater than that after the instillation of pseudo-ephedrine hydrochloride. A difference of 0.5 mm is obvious by careful inspection. The difference is maintained under a bright light. As a rule, the mydriasis with both drugs begins, reaches the maximum and disappears at the same time. In two

instances the duration of ephedrine mydriasis was several hours longer than that of pseudo-ephedrine mydriasis

*Relative Effects on Blood Pressure*—For the study of pressor action in dogs, tenth normal solutions were used, so that these drugs could be compared equimolecularly. A typical experiment is shown in figure 1. It should be noted that  $\beta$ -phenyl-ethylamine, injected intravenously has a greater intensity than, but lacks the duration of, the action shown by ephedrine. Pseudo-ephedrine has a duration of action corresponding to that of ephedrine, but is not so intense. Ephedrine in this particular experiment is 3.2 times as strong as pseudo-ephedrine. The same picture is obtained if the order of injections is reversed. In performing

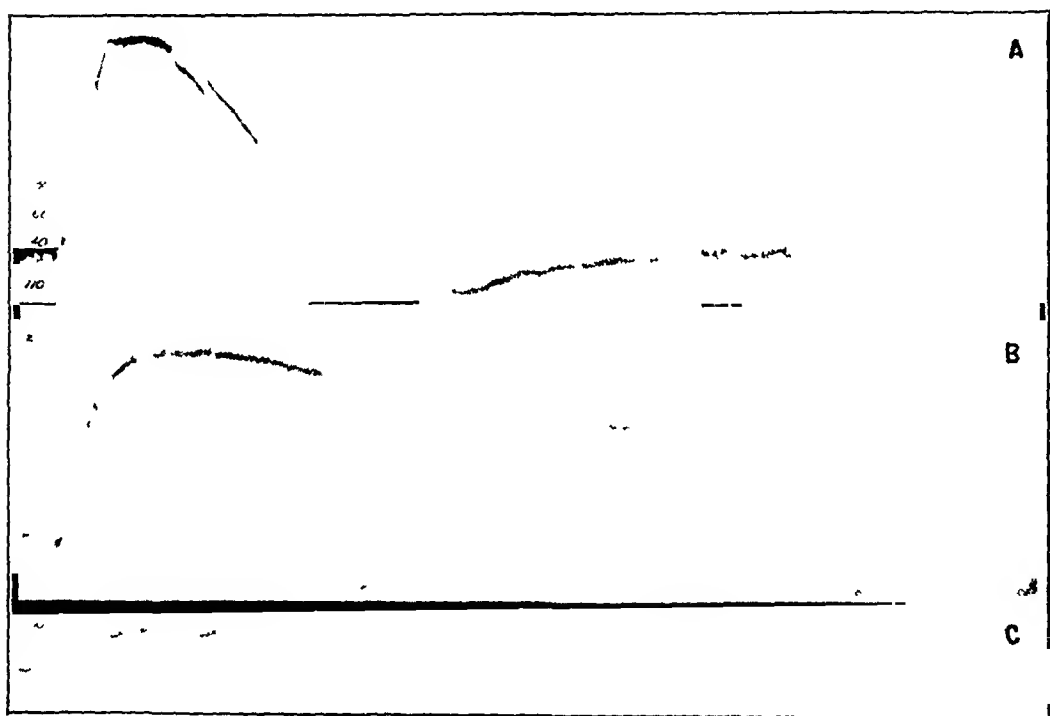


Fig 1—A comparison of effect of intravenous injection of  $\beta$ -Phenyl-ethylamine, ephedrine and pseudoephedrine in raising blood pressure in a female dog weighing 6.3 kilograms, anesthetized by phenolbarbital sodium. A, B and C indicate carotid pressure. Atropine sulphate, 1 milligram, given at start.

these experiments, the kind of anesthetic which is used appears to have a great influence. In deep ether anesthesia, the blood pressure often falls, instead of rising, following the administration of these substances. With  $\beta$ -phenyl-ethylamine, a primary brief fall may occur before the rise, possibly caused by a transient dilatation of the heart chambers.

In man, pseudo-ephedrine and  $\beta$ -phenyl-ethylamine are new drugs for internal administration, and therefore should not be used clinically until a preliminary toxicologic study is made. The minimum lethal dose of pseudo-ephedrine hydrochloride in mice as determined by Fujii<sup>8</sup> is 400 mg per kilogram. I found that the minimum lethal dose of  $\beta$ -phenyl-

ethylamine hydrochloride in rabbits is approximately 300 mg per kilogram, as shown in table 2. Death follows convulsions. On two separate occasions, I took 50 mg of each drug by mouth and experienced no discomfort of any kind. The blood pressure was not studied in this connection. I then gave the drugs, dispensed in capsules, to a group of persons, and the dose was gradually increased. The effects on the blood pressure were investigated. All of the subjects were required to stay in bed during the period of observation.  $\beta$ -phenyl-ethylamine hydrochloride, in a dosage of from 50 to 150 mg by mouth, studied in eight persons, appears not to raise the systolic blood pressure definitely, but, on the contrary, has the tendency to lower it slightly for a period of

TABLE 2—*Toxicity of  $\beta$ -Phenyl-Ethylamine Hydrochloride in Rabbits by Subcutaneous Injection*

Dose in Mg per Kg	Number of Animals Used	Number Died	Number Lived
200	2		2
250	3		3
300	2	2	
350	2	1	1
400	1	1	
450	1	1	
500	1	1	
600	1	1	

TABLE 3—*Comparative Changes of Systolic Blood Pressure in Man After the Oral Administration of 150 Milligrams, Each, of  $\beta$ -Phenyl-Ethylamine Hydrochloride, Pseudo-Ephedrine Hydrochloride, and Ephedrine Hydrochloride*

Initials	Sex*	Age	Maximal Changes in Systolic Blood Pressure in Millimeters of Mercury		
			$\beta$ -Phenyl ethylamine	Pseudo-ephedrine	Ephedrine
P O	♀	33	-10	+20	+44†
D D	♀	22	+8	-10	+26
A H	♀	32	+2	+18	+46†
E B	♀	45	-10	+10	+18
E D	♂	15	-2	+8	+28

\* In this column, ♂ indicates male, ♀, female

† Ephedrine sulphate used

from one to two hours. Pseudo-ephedrine hydrochloride, in the same dosage, similarly administered, raised the systolic pressure in nine of eleven observations on nine subjects. The rise was not so high and did not last so long as that seen after the administration of ephedrine hydrochloride. The highest level of systolic pressure effected by 150 mg of pseudo-ephedrine hydrochloride was 130 millimeters of mercury from an original level of 106, but in the same person 100 mg of ephedrine hydrochloride elevated the pressure to 140 millimeters of mercury from the same level. In two instances, there was a slight fall of blood pressure following the use of pseudo-ephedrine. The results with the three substances in five subjects produced by 150 mg dosage by mouth are shown in table 3, and those from one of them (P O) are plotted for

illustration in figure 2. The determinations in each person were made at least twenty-four hours apart. It should be noticed that  $\beta$ -phenyl-ethylamine and ephedrine were compared gram for gram. Calculated on equimolecular dosage, the amount of  $\beta$ -phenyl-ethylamine administered was larger than that of ephedrine. In two instances ephedrine sulphate, containing 77.1 per cent of ephedrine, was used instead of ephedrine hydrochloride, containing 81.9 per cent of ephedrine. There was little difference in action between sulphate and hydrochloride. No untoward symptoms occurred after the administration of 150 mg. of  $\beta$ -phenyl-ethylamine or pseudo-ephedrine, but palpitation, diaphoresis, tremor and vomiting were present, either singly or jointly, in four of the five subjects that had been given 150 mg. of ephedrine hydrochloride.

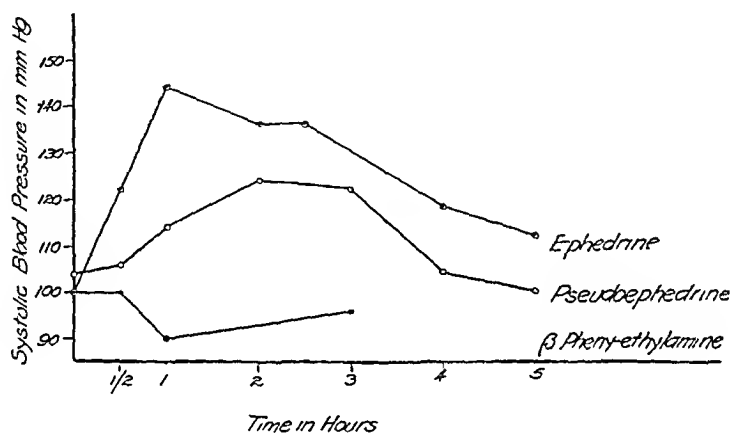
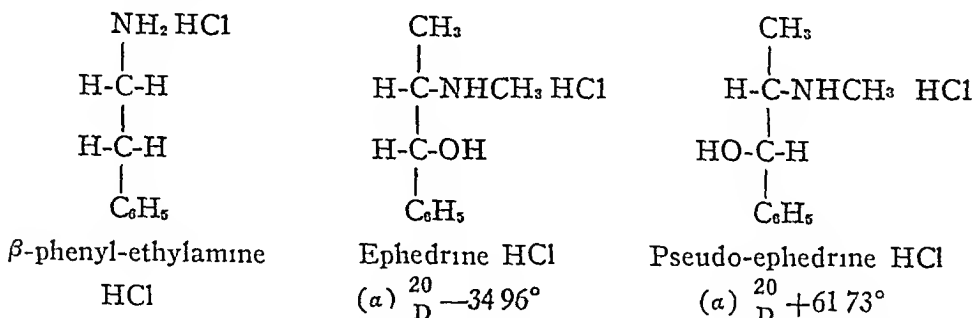


Fig. 2—A comparison of the pressor action in man of ephedrine, pseudo-ephedrine, and  $\beta$ -phenyl-ethylamine. P. O., a woman, aged 33, was given a dose of 150 milligrams of each drug by mouth.

#### COMMENT

It is true that pseudo-ephedrine and  $\beta$ -phenyl-ethylamine, like ephedrine, devoid of phenolic hydroxyls, as shown in the following formulas, are comparatively more resistant to physical agents, such as air, light



and standing, than are epinephrine and tyramine. The phenyl compounds are, as a rule, more stable than the hydroxy-phenyl compounds. In vivo, however, the blood pressure raising property of ephedrine is much more protracted than that of  $\beta$ -phenyl-ethylamine. Ephedrine and pseudo-ephedrine, on the other hand, both exert prolonged effects,

the latter being weaker than the former  $\beta$ -phenyl-ethylamine, when injected intravenously into dogs, exhibits a greater intensity of action than ephedrine, but has not the duration of action shown by ephedrine. When the solution is given by mouth, no pressor action is noted in the case of  $\beta$ -phenyl-ethylamine. Pseudo-ephedrine, the stereo-isomer having the identical structure as ephedrine, proves to be weaker in regard to both the mydriatic and the pressor action. My results in dogs and in man fully agree with those of Fujii in frogs and in rabbits. It is, then, not the absence of phenolic hydroxyls alone that characterizes the action of ephedrine. Other parts of the structure also influence the type of action. The hydroxyl group in the side chain is probably an activating factor in the ephedrine molecule. The presence of a methyl group in the  $\alpha$ -position and another methyl group in the amino radicle in the case of ephedrine and pseudo-ephedrine may not be without significance in distinguishing their action from that of  $\beta$ -phenyl-ethylamine. Probably a more important factor in the case of ephedrine and pseudo-ephedrine is the presence of asymmetrical C-atoms and the direction of optical rotation. The space relationship in ephedrine and pseudo-ephedrine must account for the difference in the intensity of action.

In 1901 Schmiedeberg,<sup>10</sup> in connection with his investigation of purine derivatives, made the statement that the intensity of pharmacologic action of a substance depends on the stereochemic configuration, while the kind of pharmacologic activity depends more on the chemical constitution. The following are his own words:

“ Alle bisher bekannten pharmakologischen Thatsachen weisen darauf hin, dass die pharmakologische Wirksamkeit einer Substanz von der stereochemischen Configuration, die Art der pharmakologischen Wirkungen dagegen mehr von der chemischen Constitution abhängig sind ”

The pharmacologic difference of two optical isomers was first carefully studied by Cushny, whose work on this subject has been concisely summarized by himself in his Dohme Lectures.<sup>11</sup> It is known that 1-hyoscyamine is about twenty times, 1-hyoscyne from sixteen to eighteen times, 1-epinephrine from twelve to fifteen times, and 1-homatropine two times, respectively, as strong as the d-form.

The formula for ephedrine and pseudo-ephedrine contains two asymmetric C-atoms. They are not mirror images of each other. Their isomerism has been discussed by Chen and Kao,<sup>12</sup> based on the work of

10 Schmiedeberg, O. Vergleichende Untersuchungen über die pharmakologischen Wirkungen einiger Purinderivate, Ber d deutsch chem Gesellsch **34** 2550, 1901

11 Cushny, A. R. Biological Relations of Optically Isomeric Substances, Baltimore, Williams & Wilkins Co., 1926

12 Chen, K. K., and Kao, C. H. Ephedrine and Pseudoephedrine, Their Isolation, Constitution, Isomerism, Properties, Derivatives, and Synthesis (with a Bibliography), J. Am. Pharm. A **15** 625, 1926

previous writers. It suffices here to point out that ephedrine is levorotatory, and has a stronger mydriatic and pressor action than pseudo-ephedrine, which is dextrorotatory. There has been added, therefore, to the category of optical isomers another example that the l-form is more powerful than the d-form.

#### CONCLUSIONS

$\beta$ -phenyl-ethylamine hydrochloride when applied locally to rabbits' and cats' eyes does not dilate the pupils.

$\beta$ -phenyl-ethylamine hydrochloride when injected intravenously into dogs in small doses (0.5-2.7 mg per kilogram) raises arterial blood pressure. The rise is more intense but less persistent than that seen after the injection of ephedrine. When given by mouth in man, it does not exhibit its pressor action.

Pseudo-ephedrine hydrochloride dilates the pupils of man when applied locally, raises arterial blood pressure in dogs when injected intravenously and slightly increases the systolic blood pressure in man when given by mouth. Pseudo-ephedrine is dextrorotatory, and is less powerful in pharmacologic activity than ephedrine, which is levorotatory.

# GLYCOLYSIS IN NORMAL AND IN LEUKEMIC BLOOD\*

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The study of the destruction of glucose by the cells of the body has recently received a new impetus through the discovery by Warburg<sup>1</sup> that tumor tissues have quantitative and qualitative differences from the normal, with regard to their carbohydrate metabolism. Warburg found that the glycolytic activity of malignant tumor tissues in human beings and in rats was many times greater than that of normal tissues when studied under aerobic or anaerobic conditions in a respiration apparatus.

Warburg's work has been largely confirmed by Murphy and Hawkins<sup>2</sup>. They have noted certain exceptions to his general conclusions and point out that glycolytic activity bears no close relationship to rate of growth. Nevertheless, they conclude that Warburg's studies have opened a new and fruitful field for research in cancer.

It seemed possible to acquire further data on the problem by the investigation of glycolysis in certain disorders of the blood—especially in the leukemias—whose character may be considered similar to that of tumors. In leukemia one has an alteration of the blood-forming tissues with the appearance of great numbers of immature blood cells which appear to have much in common with the cells of malignant tumors. Thus, this article concerns a study of *in vitro* glycolysis in blood, especially as it relates to the number and immaturity of the blood cells.

The literature on glycolysis in the blood is extensive, but the emphasis in the past has been on such aspects of it as relate to sugar metabolism. John<sup>3</sup> recently has reviewed most of the articles that appeared between Claude Bernard's original contribution in 1876 and those of later writers, up to 1925. Because of the divergence of opinion on many basic points, it became necessary, as part of the present work, to determine the glycolytic behavior of normal blood. Apparently, the only previous investigation on glycolysis in leukemia is that by Burger<sup>4</sup>.

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\* From the medical service of the Collis P. Huntington Memorial Hospital of Harvard University.

1 Warburg, O. Metabolism of Carcinoma Cells, *J. Cancer Research* **9** 148 (March) 1925.

2 Murphy, J. B., and Hawkins, J. A. Comparative Studies on the Metabolism of Malignant and Normal Cells, *J. General Physiol.* **8** 115 (Sept) 1925.

3 John, H. J. Glycolysis, *Ann. Clin. Med.* **3** 667 (May) 1925.

4 Burger, M. Untersuchungen über Hamoglykolyse, *Ztschr. f. ges. exper. Med.* **31** 1, 1923.

in 1923 He studied the glycolytic rate of the blood from seven patients However, he made observations only before and after a six hour interval, and therefore failed to observe the significant changes during the first few hours

#### MATERIAL AND METHODS

About 100 blood sugar determinations were made on blood from nine healthy persons, six patients with chronic myelogenous leukemia, and one each with chronic lymphatic leukemia, erythemia and pernicious anemia None of the leukemic patients had received roentgen-ray or radium treatment for at least a month prior to testing their blood The one with the highest white cell count had never been given such therapy

The determinations were made in duplicate on the protein-free filtrates by Folin's <sup>5</sup> new method, and often compared with the results obtained with the Folin-Wu <sup>6</sup> method

The usual procedure was to withdraw from 15 to 30 cc of blood from the arm vein under sterile precautions, no special effort being made to avoid stasis The blood was then discharged into an Erlenmeyer flask of 150 cc capacity and mixed with heparin This was transported to the incubator in a beaker of water with a temperature of 37 C The incubator temperature at which all the experiments were made ranged from 35 to 37 C

After the blood was drawn from the patient, its sugar content was determined immediately The glycolytic process was then studied by finding the amount of sugar in 2 cc samples taken from the incubator specimen at hour or half-hour intervals for five or six hours In some cases a sample was again tested at the twenty-fourth hour However, with few exceptions, the glycolysis was complete at the end of six hours when the initial sugar concentration was under 100 mg per hundred cubic centimeters

Initial experiments to test the effect of temperature showed entire concordance with the results of previous workers, namely, that lowering of the temperature slows but does not stop the glycolytic process

The literature contains numerous divergent reports concerning the effects of the ordinary anticoagulants, such as sodium citrate and potassium oxalate, on glycolysis Heparin was used because it was believed to be the anticoagulant that was least likely to damage cells or affect glycolysis Sterilization of heparin as a powder or in solution did not affect its anticoagulant properties It was readily made into a solution of which 0.05 cc was equivalent to 1 mg of the dry powder One milligram was sufficient to prevent the coagulation of 5 cc of normal blood for at least twenty-four hours Because leukemic blood in vitro often tends to clot more rapidly than normal, it usually was necessary to add about twice as much heparin as is required to prevent normal blood from clotting Control experiments with specimens of normal blood showed that this double amount of heparin did not hasten glycolysis

Separate experiments using blood kept under liquid petrolatum were performed with a view to studying the effect of low oxygen saturation No

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<sup>5</sup> Folin, O The Determination of Sugar in Blood and in Normal Urine, *J Biol Chem* **67** 357 (Feb) 1926

<sup>6</sup> Folin, O, and Wu, H A Simplified and Improved Method for Determination of Sugar, *J Biol Chem* **41** 367 (March) 1920

appreciable differences were found between the specimens of blood under oil and those freely exposed to air

Most of the experiments were not performed with strict asepsis, as the period of the experiment (from one to six hours after withdrawal) precluded any significant bacterial growth. However, enough aseptic controls were examined to show that the results were in no way altered by sterilization of the materials in contact with the blood. The asepsis was proved to be complete by making pour plates of blood with hormone agar, incubating for from twenty-four to forty-eight hours and finding no bacterial growth.

Folin's new blood sugar method<sup>5</sup> gives somewhat lower values than the Folin-Wu<sup>6</sup> method. However, either method was found satisfactory for

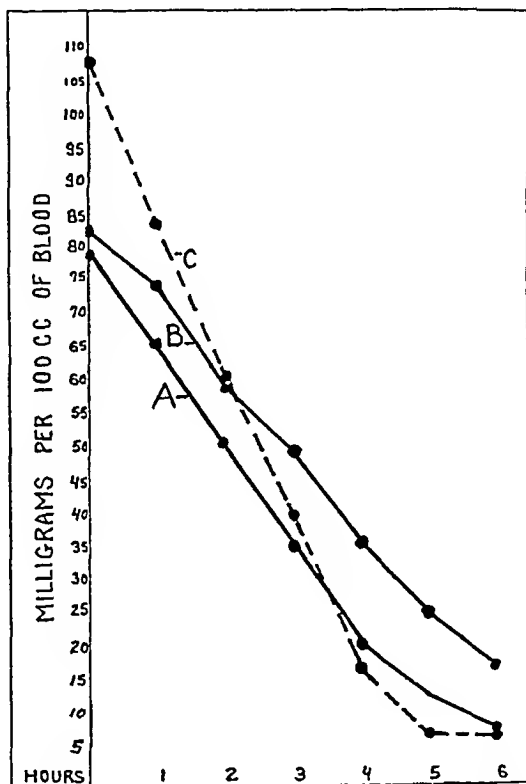


Chart 1—Glycolysis in normal blood in vitro. A, average rate for six different specimens of blood, B and C, rate in blood from one person when the blood sugar was at different levels

reading blood sugar contents as low as 10 mg per hundred cubic centimeters, provided weaker standards than usual were used. In addition to the customary ones containing 0.2 and 0.1 mg of glucose per cubic centimeter, standards of 0.05 mg and 0.025 mg per cubic centimeter were utilized for the blood sugar ranges of from 50 to 6 mg per hundred cubic centimeters of blood. The standards were frequently checked and new ones made about once a week to avoid deterioration.

The blood specimens of the patients with leukemia were drawn in a fasting state, but this did not seem an integral part of the experimental conditions. However, most of the other blood specimens were obtained at such an interval after meals as to have a blood sugar content approximately that of the fasting level. There were two experiments in which a hyperglycemia was produced by the injection of epinephrine hydrochloride.

## GLYCOLYSIS IN NORMAL BLOOD

Chart 1 *A* shows the average rate of glycolysis in the blood of six normal persons. The red blood corpuscles numbered about 5,000,000 and the white blood cells about 8,000 per cubic millimeter.

The graph shows that the glycolysis proceeded at a uniform, predictable rate for the first four hours. The same was true for many of the individual blood specimens as well as for the average of all. At the sixth hour, the blood sugar had usually fallen to 6 or 8 mg per hundred cubic centimeters of blood. This level represents the end of the process so far as the glycolyzable reducing substances of the blood are concerned. When the Folin-Wu method was used, the lower limit usually was about 17 mg. Prolonged standing of the blood, even for twenty-four hours, did not reduce further the value obtained by either method. It probably represents the nonglucose substances of the blood which reduce the copper reagents.<sup>7</sup>

The effect of varying the initial sugar concentration was studied, using blood from the same healthy person. The initial experiment (chart 1 *B*) determined the rate of glycolysis when the subject's blood sugar level was 82 mg per hundred cubic centimeters of blood. In the next one (chart 1 *C*) the blood was drawn one hour after the ingestion of 50 Gm of carbohydrate when the blood sugar was 107 mg. If the curves are superimposed, it is evident that the process was more rapid in the latter. This is an important comparison because some investigators have reported that glycolysis is either always unaffected by hyperglycemia or that it always proceeds more rapidly with a low initial concentration.<sup>8</sup> The reason for their lack of consonance with this report is partly found in their utilization of percentage loss from the start instead of the loss in absolute milligrams. As Cajori and Crouter<sup>9</sup> have pointed out, the glycolytic reaction is not a monomolecular one, and it is therefore improper to express results in terms of percentage loss from the original concentration. Chart 1 clearly shows that the rate should be expressed absolutely and not in percentage. The original concentrations are different enough (25 mg) to test the effect of changed concentrations, and yet near enough together so that one may observe how the glycolysis in the hyperglycemic blood may proceed faster than in the blood with less sugar. The greatest variations in the normal blood were outside the range of the pathologic blood studied.

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7 Hiller, A., Lindner, G. C., and Van Slyke, D. D. The Reducing Substances of the Blood, *J Biol Chem* **64** 625 (July) 1925.

8 Lemann, I. I., and Liles, R. T. Glycolysis at Varying Blood Sugar Levels, *J Lab & Clin Med* **11** 339 (Jan) 1926.

9 Cajori, F. A., and Crouter, C. V. A Comparison of the Rate of Glycolysis in Different Bloods with Special Reference to Diabetic Blood, *J Biol Chem* **60** 765 (July) 1924.

The fasting blood sugar values for the seven cases of leukemia were within normal limits. In all seven of the leukemic blood specimens glycolysis proceeded faster than normal, and in the six chronic myelogenous leukemic blood specimens at least twice, and in some cases three times, as fast as normal. Chart 2 illustrates the observations and shows that in leukemia the process may be complete in a little more than one hour, as contrasted with six hours for the normal. The slowest of these abnormally rapid rates occurred in the blood of the patient with chronic lymphatic leukemia (chart 2 *B*). This person had the lowest white cell count of all seven patients, namely, 30,000 per cubic millimeter, composed chiefly of lymphocytes, of which 11,000 per cubic millimeter were somewhat, though not markedly, immature. Numerous investigators have pointed out that the white blood cells play an important rôle in glycolysis. The observations recorded here show that the most rapid rates were observed in the cases with the highest white cell counts. However, the height of the total count alone may not be entirely responsible for the increase of rate in leukemic blood since the number and type of immature cells present may play some rôle.

The observations are too few to permit proof of this suggestion, but the facts recorded below bear on the problem. The glycolytic rate in case *E* (chart 2), of myelogenous leukemia, in which there was a white cell count of 51,000 per cubic millimeter, was much more rapid than that of the case of chronic lymphatic leukemia with 30,000 white blood cells per cubic millimeter (chart 2 *B*). In the former case there were not only more immature white cells than in the latter, but they were of bone marrow, not lymphoid, origin. Likewise, many of the myeloid cells were most immature (myeloblasts) and some of an atypical abortive sort, while in the blood of the patient with lymphatic leukemia there were essentially no such immature cells. The difference in rates might be attributed to a distinction between myeloid and lymphoid cells, but the greater degree of immaturity and greater numbers of young cells in the blood in the myelogenous leukemia could better explain its rapid glycolytic rate. Furthermore, the rate in the blood in this case of chronic myelogenous leukemia was faster than that in two other cases with a white cell count two or three times as high (chart 2 *C* and *D*). In the latter blood there were almost no grossly immature or abortive types of white cells, although the absolute number of cells as immature as myelocytes was greater. This might be taken to indicate that a given number of markedly immature cells (myeloblasts) will influence the process more than a similar number of less immature cells (myelocytes). The rates were rapid in cases *F*, *G* and *H*, and this fits well with both their high total counts and large number of myeloblasts. The low

initial sugar level in cases F, G and H may have had a tendency to slow the process, as compared with normal blood, so that here also we have confirmatory evidence of a definite effect of the leukemic blood

The white cell counts in cases C, D, E, F, G and H are shown in the table

If the lowness of the level of the red blood corpuscles influences glycolysis, it probably delays, not hastens, the process The two leukemic

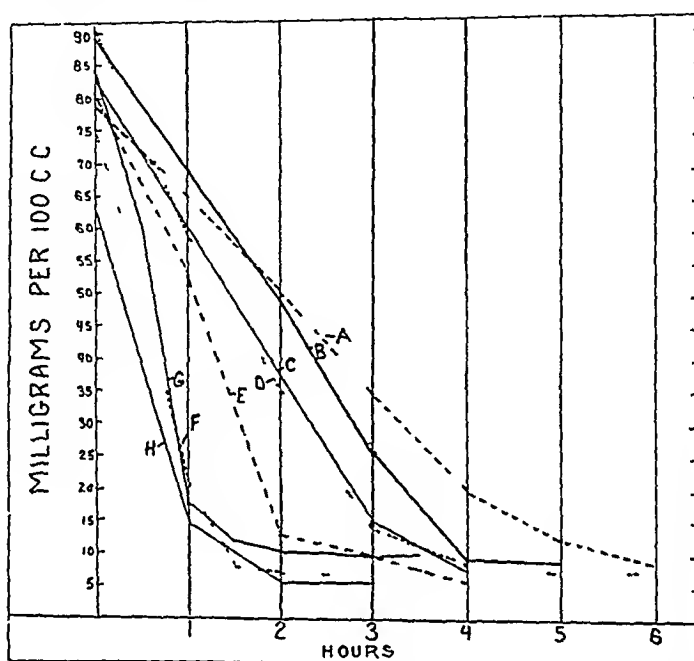


Chart 2—Glycolysis in leukemic blood in vitro A, normal blood (average), B, chronic lymphatic leukemia The white blood cells totaled 30,000, of which 80 per cent were lymphocytes, 11,000 per cubic millimeter, were somewhat, but not markedly, immature C, D, E, F, G and H, chronic myelogenous leukemia

#### White Cell Counts in Cases of Leukemia

Case	Total White Cell Count per C Mm	Total Immature Cells (Myelocytes or Younger), per C Mm	Markedly Immature Cells (Myeloblasts), per C Mm
C	105,000	23,100	100
D	161,000	38,000	100
E	51,000	15,800	3,500
F	130,000	39,000	1,960
G	219,000	60,300	8,700
H	368,000	87,600	10,300

patients that had the lowest red cell counts (3,500,000 per cubic millimeter) were those that had the white cell counts of 51,200 (chart 2 E) and 368,000 per cubic millimeter (chart 2 H), and whose blood contained numerous immature and atypical cells Thus, anemia in itself presumably did not hasten the glycolysis in the blood in these two patients

The glycolytic rate was compared in normal and in leukemic blood with a high sugar content produced by the injection of epinephrine hydrochloride (chart 3). It was found that while the rate of sugar destruction in the leukemic blood eventually overtook that of the normal, nevertheless, the raising of the initial sugar concentration served to make the velocity of the normal blood quite high. The part that may have been played by the epinephrine hydrochloride or such substances as it set free in the body is unknown. The glycolytic rate was studied in the blood from the same leukemic patient during the fasting state

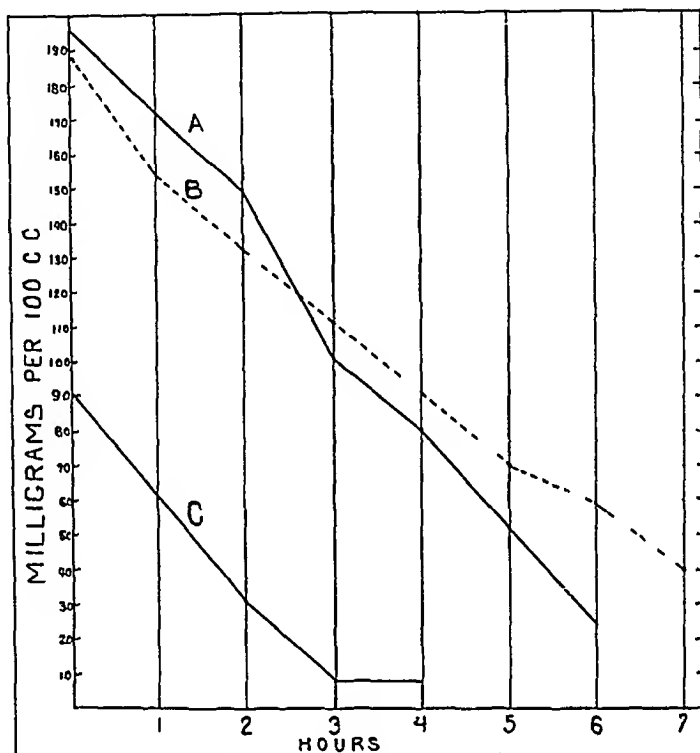


Chart 3—Rate of glycolysis in blood with high initial sugar content produced by hypodermic injection of epinephrine hydrochloride. *A*, blood from patient with chronic myelogenous leukemia, *B*, normal blood, and *C*, blood from the same subject as *A* withdrawn before the injection of epinephrine hydrochloride (fasting level)

If the curve for the latter rate is compared with the one for the data obtained when hyperglycemia existed (chart 3) by superimposing the two at the same blood sugar level (90 mg), the rates are found to be approximately the same.

#### GLYCOLYSIS IN BLOOD WITH REFERENCE TO THE RED BLOOD CELLS

The influence of the number and type of red blood corpuscles on glycolysis was studied only by testing the blood in a case of erythremia in which there were 9,505,000 red blood cells per cubic millimeter and in

a case of pernicious anemia, in mild relapse, in which there was a red blood cell count of 2,830,000 per cubic millimeter. In the former case, the white cell count was 25,775 per cubic millimeter and 88 per cent of the cells were polymorphonuclear neutrophils, in the latter case, there were 4,000 white blood cells per cubic millimeter and 64 per cent were polymorphonuclear neutrophils. The rate of glycolysis in the erythremic blood was considerably accelerated, being faster than in the blood from the patient with lymphatic leukemia with a white cell count of 30,000 and a red blood cell count of 4,000,000 per cubic millimeter. The initial blood sugar was 15 mg greater than in this leukemic blood, or 115 mg per hundred cubic centimeters. The height of the blood sugar does not seem great enough to account for the more rapid rate. The blood sugar dropped rapidly in an hour to 65 mg and to 30, 12 and 6 mg at the end of two, three and four hours, respectively. In contrast to this, the rate of glycolysis in the blood in the case of pernicious anemia was slower than that shown in any one of the six normal blood specimens. The initial sugar concentration was 30 mg less than that of the erythremic blood, or 85 mg per hundred cubic centimeters. This difference can partially, but not entirely, account for the much faster glycolytic rate of the blood in the case of erythremia than in that in the case of pernicious anemia. The sugar in the latter blood was reduced to 41 mg at the end of three hours and 13 mg in six hours. The increased absolute number of nucleated cells in the erythremic blood may have partially caused the increased velocity of glycolysis, and their sparse number in the blood in the case of pernicious anemia may account in a measure for its slow glycolytic rate. It seems more probable that the rates were in some manner dependent on the fact that the blood of one patient contained 6,000,000 more red cells per cubic millimeter than that of the other. The percentage of reticulocytes (young red cells) was similar (about 3 per cent) in the blood of both persons. Their absolute numbers may have played a rôle in the rate of glycolysis, as well as the nature of all the red blood corpuscles in each blood, for these are of a distinctly different kind in erythremia and pernicious anemia. Further studies may show more clearly how the number and character of the red blood corpuscles influence the velocity of glycolysis. The blood platelets, too, may share in the process.

#### GLYCOLYSIS IN PLASMA AND IN BLOOD TO WHICH WATER HAS BEEN ADDED

Because opinions differ as to the progression of glycolysis in plasma and in hemolyzed blood, experiments were carried out to test these points. In one case, the blood from a patient with chronic myelogenous leukemia was utilized. This had previously been studied in the usual fashion and essentially all the sugar was observed to disappear within

one and one-half hours. However, in the plasma alone there was absolutely no change in the sugar concentration from the initial figure of 71 mg for at least five hours. A specimen examined at the twenty-fourth hour showed that the process had gone on to completion, the sugar level then being near the usual base line of 6 mg. This observation may reconcile divergent views and should be investigated further.

To study the effect of cellular disintegration, seven volumes of water were added to a specimen of blood from the patient with erythremia, thus hemolyzing the red blood cells. Here, again, no glycolysis was observed for five hours. The specimen was not tested at the twenty-fourth hour.

Apparently, therefore, intact red or white blood cells are essential for relatively rapid glycolysis. Many writers in the past have incorrectly considered that the addition of water to blood affected only the red cells. This is not a valid conception because the leukocytes are susceptible to markedly hypotonic solutions.

Because of the limited number of observations and patients, some of the information presented in this article is fragmentary. It is, however, presented now as circumstances prevent additional studies for some time.

#### SUMMARY AND CONCLUSIONS

Glycolysis in normal blood *in vitro* at body temperature is complete in six hours when the initial sugar concentration is under 100 mg per hundred cubic centimeters.

Glycolysis in the blood in six cases of chronic myelogenous leukemia with a high white blood cell count was from two to three times as rapid as normal, so that the process was often complete in two hours. The large number of white blood cells may not be the only reason for the rapid glycolysis. There is some evidence to suggest that very immature or atypical bone marrow cells hasten the process more than mature or typical ones. Lymphocytes may influence the rate differently from nucleated bone marrow cells.

In the blood in one case of erythremia, glycolysis took place more rapidly than in normal blood. In contrast, in the blood from a case of pernicious anemia, glycolysis was slower than in normal blood.

Glycolysis in plasma alone or in blood after injury to the cells by water was much slower than in intact blood prevented from clotting with heparin.

# THE RED CELL COUNT IN ARTHRITIS

## FIRST PAPER <sup>2</sup>

E G PEIRCE, M D

AND

RALPH PEMBERTON, M D

PHILADELPHIA

In a series of previous communications, the suggestion has been advanced by Pemberton,<sup>1</sup> and evidence has been deduced by Pemberton, Cajori and Clouter,<sup>2</sup> that the arthritic and rheumatoid syndrome is accompanied by disturbances of the peripheral blood flow apparently in the capillary beds, and apparently in the nature of vasoconstriction. It became desirable, therefore, to determine whether, at the periphery, any reflection of this condition could be obtained in the corpuscular elements of the blood in regard to morphology, number or other factors. It seemed possible that some reflection of any circulatory disturbances present in arthritis might be obtained by studying the blood first issuing after a quick stab of moderate depth and by contrasting it with the subsequently appearing blood representative of the general circulation.

The observations here reported were made accordingly during a study of the red cell counts of patients with arthritis as compared with the red cell counts of normal persons, observations were also made on arthritic patients in various stages of ill health and convalescence. Reference to standard textbooks on clinical diagnosis shows that distinction is not always made between the blood first issuing after the conventional stab for a blood count and that issuing subsequently. Thus, Emerson states <sup>3</sup> "After the ear or finger has been pricked deeply so that the blood flows freely without the assistance of pressure, a large drop is allowed to collect on the skin and is rapidly drawn into the pipet to the mark 0.5 or 1, according to the condition of the blood."

According to Webster,<sup>4</sup> "As soon as a good sized drop appears which is obtained without pressure or constriction, the tip of the pipet

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<sup>1</sup> From the Laboratory of Clinical Chemistry, Presbyterian Hospital, Philadelphia.

<sup>2</sup> The work here reported is part of a study on Chronic Arthritis in collaboration with R. B. Osgood, M.D., of Boston. The expenses were defrayed by contributions from several sources, including a number of patients.

<sup>1</sup> Pemberton, R. Effects of External Heat Upon Human Body, *Am J M Sc* **169** 485 (April) 1925.

<sup>2</sup> Pemberton, R., Cajori, F. A., and Crouter, C. Y. Influence of Focal Infection and Pathology of Arthritis, Results of Experiments, *J A M A* **85** 1793 (Dec 5) 1925.

<sup>3</sup> Emerson, C. P. Clinical Diagnosis, Philadelphia, J. B. Lippincott Co., 1921, p. 456.

<sup>4</sup> Webster, Ralph W. Diagnostic Methods, ed. 4, Philadelphia, P. Blakiston's Sons & Co., 1920, p. 515.



uniform time after ingestion of food and under uniform conditions of exercise and environmental temperature. The fingers of the patient were allowed to rest on a laboratory table and were not grasped or encircled by the hand of the examiner. The stab was made half way between the ball of the finger and the most distal point of the palmar surface. Hausser's Neubauer double ruled counting chamber and "Bureau of Standards" pipet and covers were used throughout the experiment. Toisson's diluting fluid was employed. The instrument used for the stab was a heart-shaped lance so held that the blade was at right angles to the long axis of the finger in order that the maximum number of capillaries might be cut. The fingers were gently cleansed with alcohol, avoiding unnecessary evaporation and chilling of the part. To obtain the contrast between the red cell count of the first and fourth or subsequent drops, the first stab was so made as to obtain a slow flow and a drop which could be drawn into the pipet as the blood emerged from the finger. Considerable practice is necessary to avoid obtaining either too little blood or so much that the drop rapidly becomes too large to be drawn into the pipet. This event indicates a free bleeding from deeper or larger vessels. Only such blood should be used as comes supposedly from the immediately underlying tissue and is not mixed with, or rapidly forced out by, a larger current behind it. By the time the pipet had been shaken for two minutes during our experiments, the original stab had usually ceased to bleed. In such cases a deeper stab was made in the same general manner in another finger.

In order to obtain the more freely flowing blood, three drops were allowed to issue from the first or second stab, they were gently wiped off, and the fourth drop was used for a count. In all cases the pipet was shaken for five minutes by hand in a direction at right angles to the long axis of the pipet. The counting chamber was then filled in the manner recommended. Both sides of the chamber were counted, making a total of eight squares of twenty-five small squares each, or 200 small squares in all.

It is interesting to observe, as a check on the general observations to be described presently, that it was often difficult to make the patients with arthritis bleed adequately under the conditions described for obtaining the first drop. It was frequently necessary to prick several fingers and even to prick deeply before blood could be obtained. This was seldom the case with normal persons.

There was often a great discrepancy between the red cell counts thus made, on either the first or fourth drops, and those made in the general clinical laboratory of the hospital on the same patient. The counts of the hospital technicians were almost invariably lower. This was accounted for by the fact that it was sometimes difficult or impossible to obtain a freely flowing drop from the patient with arthritis, and

in consequence it appeared necessary for the hospital technician to squeeze the finger to obtain sufficient blood. In the present series some cases were eliminated because it was impossible to obtain blood without making such pressure, and only those cases were studied in which the blood appeared without squeezing. It was impossible to avoid the impression that the patients with arthritis sometimes presented an apparently "desiccated" condition, particularly in the more severe cases.

It is to be expected that a procedure which involves a method so commonly employed as that of counting blood will attract others to repeat this work. It is desirable and necessary that it should. The difficulty of obtaining a dependable and uniform technic, however, is much greater than appears on the surface, and results cannot be regarded as acceptable unless and until the operator is able consistently to obtain counts on the same person at the same sitting within variations of 150,000 cells. Unless care is exercised and experience obtained far beyond the level of routine practice, the observations reported here cannot be expected to be observed, and it is deemed of great importance to issue this note of warning. It is necessary to emphasize that observations of this nature cannot be conducted incidentally to routine clinical work. Some of the difficulties of repetition at the hands of others, together with the results of attempts at substantiation by other methods and other observers, will be given in a subsequent paper.

In order to avoid being misled, minor differences in contrast observations on first and later drops, varying from each other by less than 100,000, are regarded as showing no difference. The subjoined tables represent red cell counts on normal persons, patients with mild arthritis and patients with severe arthritis, respectively. In table 1, it will be seen that in twenty-three contrast counts on seventeen normal subjects, seventeen observations showed a higher cell count in the first drop issuing than in the later drops, an incidence of 74 per cent. In table 2, fifteen contrast counts on thirteen patients with mild arthritis, show ten observations in which the red cell count was higher in the first than in later drops, an incidence of 67 per cent.

In table 3, however, forty-four contrast counts on thirty-seven patients show only nine observations in which the red cell count of the first drop was higher than in the later drops, an incidence of 20 per cent. On the other hand, twenty-one observations showed a red cell count of the first drop lower than that of subsequent drops by an amount equal to or greater than 100,000 cells per cubic millimeter. This is an incidence of 48 per cent and is in contrast with the counts made for normal persons and for the patients with mild arthritis, many of the latter of whom were recovered or essentially well. The lower first counts for normal persons and for patients with mild arthritis were, respectively, 4 per cent and 20 per cent.

This lower count in the first issuing blood, or for sake of abbreviation, "minus first drop," may be to some degree a function of inactivity but is not wholly so, since the greatest difference observed was in a patient with spondylitis, a young man who was thoroughly active at the time and gave a minus drop of 1,144,000 The next greatest difference

TABLE 1—*Blood Counts in Normal Persons Comparing the Red Cell Count in the First Drop with That in Subsequent Drops*

	First Issuing Drop of Blood	Subsequently Issuing Drops	Difference in Red Cell Count	Remarks
Wright	4,632,000	4,452,000	180,000+	
L-d-l	4,680,000	4,512,000	168,000+	
M-rsh-ll	4,512,000	4,068,000	444,000+	
Lewis	5,392,000	5,080,000	312,000+	
M-nie	4,508,000	4,028,000	480,000+	
F-lks	4,460,000	4,068,000	392,000+	
Livingston	4,460,000	4,224,000	136,000+	
C-j-i	5,112,000	4,824,000	288,000+	
	5,208,000	4,440,000	768,000+	
	5,336,000	4,928,000	408,000+	
Crouter	4,024,000	3,888,000	136,000+	
Pemberton	5,024,000	4,880,000	144,000+	
Clark, Jr	4,184,000	3,888,000	296,000+	
Crouter	4,640,000	3,592,000	1,048,000+	
Palladino	4,976,000	4,620,000	356,000+	
Grove	4,144,000	3,660,000	484,000+	
Hunter	5,288,000	5,272,000	16,000+	No difference
Seem	4,684,000	4,632,000	52,000+	No difference
Bassett	4,896,000	4,936,000	40,000—	No difference
Kaufman	4,088,000	4,360,000	272,000—	Hands cold and white
C-j-i	4,712,000	4,808,000	96,000—	No difference
	5,000,000	5,008,000	8,000+	No difference
	5,352,000	5,014,000	308,000+	

There were 17 subjects, 23 double counts, 10 first drop counts were plus, an incidence of 74 per cent, 1 first drop was minus, an incidence of 4.35 per cent

TABLE 2—*Blood Counts in Patients with Mild Arthritis Comparing the Red Cell Count in the First Drop with That in Subsequent Drops*

	First Issuing Drop of Blood	Subsequently Issuing Drops	Difference in Red Cell Count	Remarks
Cro-ter	4,260,000	4,592,000	332,000—	
Peirce	4,504,000	4,028,000	476,000+	
	4,504,000	4,200,000	304,000+	
	4,384,000	4,048,000	336,000+	
Roberts	5,080,000	4,544,000	536,000+	
Beal	5,152,000	4,824,000	328,000+	
Roberts	5,096,000	4,650,000	446,000+	
Jones	5,160,000	5,464,000	304,000—	
Gifford	3,888,000	3,920,000	32,000—	No difference
Handy	4,432,000	4,376,000	56,000+	No difference
Pearce	4,200,000	4,016,000	184,000+	
Reiter	5,064,000	4,796,000	268,000+	
H-st-ter	3,976,000	4,632,000	656,000—	
Jones, Mrs	4,320,000	4,220,000	100,000+	
Proctor	4,640,000	4,416,000	224,000+	

There were 13 patients, 15 double counts, 10 first drop counts were plus, an incidence of 67 per cent, 3 first drop counts were minus, an incidence of 20 per cent

ence (—604,000) was in the case of an invalid on crutches who, however, had had vigorous massage and many active exercises daily Among other cases, Hanold (—224,000) was physically active and engaged in business Coyle (—352,000) was the active mother of a large family On the other hand, Corbitt, the least active, being bed-fast, had a red cell count of +240,000 None had reached extreme

cases of deformity, all could feed themselves, and all, except Corbitt, K-n-l-d and A-d-r-t-n, could move about

It is to be appreciated that small differences of, say, 50,000 may be caused by the variations inherent in the method of blood counting, but counts which show consistently a difference of 100,000, in a direction opposite to the normal trend, under the conditions of the experiment cannot be attributed to error of technic or to the personal equation

TABLE 3—*Blood Counts in Patients with Severe Arthritis Comparing the Red Cell Count in the First Drop with That in Subsequent Drops*

	First Issuing Drop of Blood	Subsequently Issuing Drops	Difference in Red Cell Count	Remarks
Botts	3,800,000	4,376,000	576,000—	
	3,664,000	4,024,000	360,000—	
K-n-l-d	3,848,000	4,096,000	248,000—	
Cl-rl	3,752,000	4,056,000	304,000—	
Corbitt	4,812,000	4,572,000	240,000+	
Al-xander	3,592,000	3,632,000	40,000—	No difference
Bubb	4,488,000	4,088,000	400,000+	
Milligan	4,488,000	4,092,000	396,000+	
A-d-r-t-n	4,928,000	4,648,000	280,000+	Bled with great difficulty
Russel	4,160,000	4,712,000	552,000—	
Sefton	3,992,000	4,076,000	84,000—	No difference
Coyle	3,892,000	4,244,000	352,000—	
Vorhees	3,820,000	4,112,000	292,000—	
Connell	4,584,000	4,264,000	320,000+	
Taylor	5,200,000	5,736,000	536,000—	
Hanold	4,528,000	4,752,000	224,000—	
D Roberts	4,128,000	5,272,000	1,144,000—	
	4,976,000	5,016,000	40,000—	No difference
Knott	4,704,000	4,836,000	132,000—	
Lowrie	3,976,000	3,728,000	248,000+	
Segal	4,760,000	4,856,000	96,000—	No difference
Wyatt	3,140,000	3,296,000	156,000—	
Mattson	4,568,000	4,582,000	14,000—	No difference
Rowe	4,384,000	4,988,000	604,000—	
McDowell	4,216,000	4,032,000	184,000+	
Stall	4,240,000	4,264,000	24,000—	No difference
St-nberg	3,800,000	3,952,000	152,000—	
Nabb	4,072,000	4,272,000	200,000—	
Stockdale	4,880,000	4,936,000	56,000—	No difference
Inglesby	3,612,000	3,928,000	316,000—	
Strech	4,804,000	4,720,000	84,000+	No difference
Evans	4,688,000	4,784,000	96,000—	No difference
Phillips	4,208,000	4,428,000	220,000—	
Mattson	4,752,000	4,544,000	208,000+	
Ewing	4,912,000	5,176,000	264,000—	
Dougherty	4,808,000	5,200,000	392,000—	
Sullivan	4,604,000	4,700,000	96,000—	No difference
Vorhees	4,336,000	4,344,000	8,000—	No difference, poor subject, gets excited easily
	4,908,000	4,764,000	144,000+	
P-xton	4,628,000	4,664,000	36,000—	No difference
Coogan	4,316,000	4,252,000	64,000+	No difference
Silverman	5,132,000	5,172,000	40,000—	No difference
Bubb	4,328,000	4,524,000	196,000—	
Sullivan	4,104,000	4,316,000	212,000—	

There were 37 patients, 43 double counts, 21 first drop counts were minus, an incidence of 49 per cent, 9 first drop counts were plus, an incidence of 21 per cent

It appears, therefore, that a difference has been demonstrated in the number of red cells per cubic millimeter of blood first issuing from peripheral tissues, such as the finger, in the patient with severe arthritis as compared with later issuing blood. While this difference sometimes obtains among normal persons and patients with mild arthritis, it does so with less frequency. The explanation of the cause of the higher count in the first blood of normal persons is presumably due to the fact that the capillaries are normally open in large numbers, and that the

cells within them are subject to an apparent concentration from resorption of the nutrient plasma into the tissues

Two explanations may be given of the lower count of the first drop in arthritis, namely, that the first issuing blood is diluted in the vessels, or that normal or decreased numbers of cells in the vessels are scattered by, and dispersed through, increased or normal amounts of serous fluids from the tissues as they issue forth. From the previous studies already quoted, indicating a disturbance of the peripheral blood flow in arthritis in the nature of vasoconstriction, it would appear that an explanation based on this conception is preferable. It is presumably the case in constricted vessels that fewer cells are contained within the lumen, and on section of such vessels fewer cells issue forth. The condition of capillaries and capillary beds throughout the body is notoriously open to many influences, and these vessels present at various sites at the same moment varying degrees of dilatation, collapse and constriction. The

TABLE 4—*The Red Cell Count Before and After the Ingestion of Coffee*

	First Issuing Drop of Blood	Subsequently Issuing Drops	Difference in Red Cell Count
Mattson—Before coffee at 7 30 a. m., had been quiet since waking up	4,120,000	4,224,000	104,000—
Coffee given just after blood ob- tained for count above, 8 10 a. m.	4,896,000	4,600,000	296,000+
Increase in red blood cells	776,000	376,000	
Evans—8 a. m. Before taking coffee, was resting quietly	4,072,000	4,248,000	176,000—
After coffee, 8 40 a. m.	4,920,000	4,812,000	608,000+
Increase in red blood cells	848,000	64,000	

work of Krogh, Cannon and others has amply demonstrated this as well as the influence of such measures as stroking and massage toward changing the state of dilation of any capillaries at any given time. In a case showing on one occasion a minus first drop a subsequent count on some removed occasion may reveal an increase in the count of the first drop with or without a commensurate rise in the count of the fourth drop.

In the same connection it is of interest to note in a preliminary way that in some observations by the present authors, the effect of exercise and the drinking of coffee has been to increase in a few moments the count of the first drop, and, in the case of coffee, to change the minus first to a plus first drop (tables 4 and 5). The count of the fourth drop generally increases also, though not so markedly.

This observation tends to corroborate the existence of a lesser number of cells in the first drop of the blood of patients with arthritis since it shows that suitable measures may restore it to normal. It is also particularly significant in view of the fact that exercise and the ingestion of coffee, especially the former, are potent factors in the temporary

amelioration of the subjective and objective disabilities of many patients with arthritis Especially is this true in the early morning hours when the circulation of all persons is lowest, and when patients with arthritis are at their worst

Considering in one group fifty-nine observations on fifty patients with arthritis, both mild and severe, a minus first drop or lower count in the first issuing blood was encountered in twenty-four cases, or 41 per cent

SUMMARY

A difference can be demonstrated in the number of red cells per cubic millimeter of blood first issuing from a stab of the finger in the patient with arthritis as compared with later issuing blood, in that the count made from the first blood tends to give lower figures While

TABLE 5—*The Red Cell Count Before and After Exercise*

	First Issuing Drop of Blood	Subsequently Issuing Drops	Difference in Red Cell Count
White—Rested, lying down an hour after midday meal, then exercised vig- orously for ten minutes without perspiring			
Before	4,116,000	3,924,000	192,000+
After	4,326,000	4,776,000	450,000—
Increase in red blood cells	210,000	852,000	
C-J-r—Rested one half hour before first count, then exercised vigorously ten minutes without perspiring			
Before	4,712,000	4,808,000	96,000—
After	5,476,000	5,364,000	112,000+
Increase in red blood cells	764,000	556,000	

this difference also obtains among normal persons and among patients with mild arthritis, it does so with less frequency This observation is interpreted as indicating altered circulatory conditions in arthritis, probably in the nature of vasoconstriction, and is in line with other evidence to the same end It is also evident that, even in normal persons, the drop of blood first appearing, especially if the stab is shallow, does not necessarily yield a blood count representative of the general circulation and should be discarded Reference to the standard textbooks shows that this precaution is not observed generally

Tables 4 and 5 show clearly that the cell counts of the first and freely flowing drops can be influenced in the direction of an increase It follows, therefore, that in the absence of such influence many capillaries, even in normal persons, are closed or clogged The tendency described in the patient with arthritis is doubtless an exaggeration of this condition

# THE RED CELL COUNT IN ARTHRITIS

## SECOND PAPER \*

CAROLINE Y CROUTER, M S

AND

F A CAJORI, P H D

PHILADELPHIA

The difference in the erythrocyte count of the first drop of blood as compared with subsequent drops of blood issuing from the lanced finger of a normal person has been described in the preceding article <sup>1</sup> The reversal of this difference, observed in patients with chronic arthritis, lends special interest to this subject and suggests the existence of an abnormal peripheral circulatory condition in these patients For this reason it seemed desirable to check the observations of Peirce and Pemberton independently and, if possible, by other methods This was particularly appropriate in view of the fact that many of the differences in blood count reported by them are of about the same magnitude as is the error of the method used in the red cell count

In the hope of checking up the work by entirely independent means the problem was attacked in various ways Differences in the red cell content of specimens of blood would be accompanied by differences in certain of the physical and other properties of the blood For this reason the first and freely flowing drops were compared as to specific gravity total solids, relative viscosity, iron content and intensity of spectral bands

The technic for collecting the specimens of blood developed and described in the previous article was followed scrupulously

Benzylbenzoate and cottonseed oil mixtures were employed for determination of the specific gravity, as suggested by Rezinkoll <sup>2</sup> The total solids were determined from the loss in weight of blood collected on filter paper and dried at 110 C A Hess viscosimeter was used to measure the relative viscosity These methods were not sufficiently accurate to reflect the small differences in red cells present in the specimens of blood, and were therefore abandoned Attempts were then made to measure the concentration of the red cells in the first and freely flowing drops by a colorimetric determination of the iron content Brown s

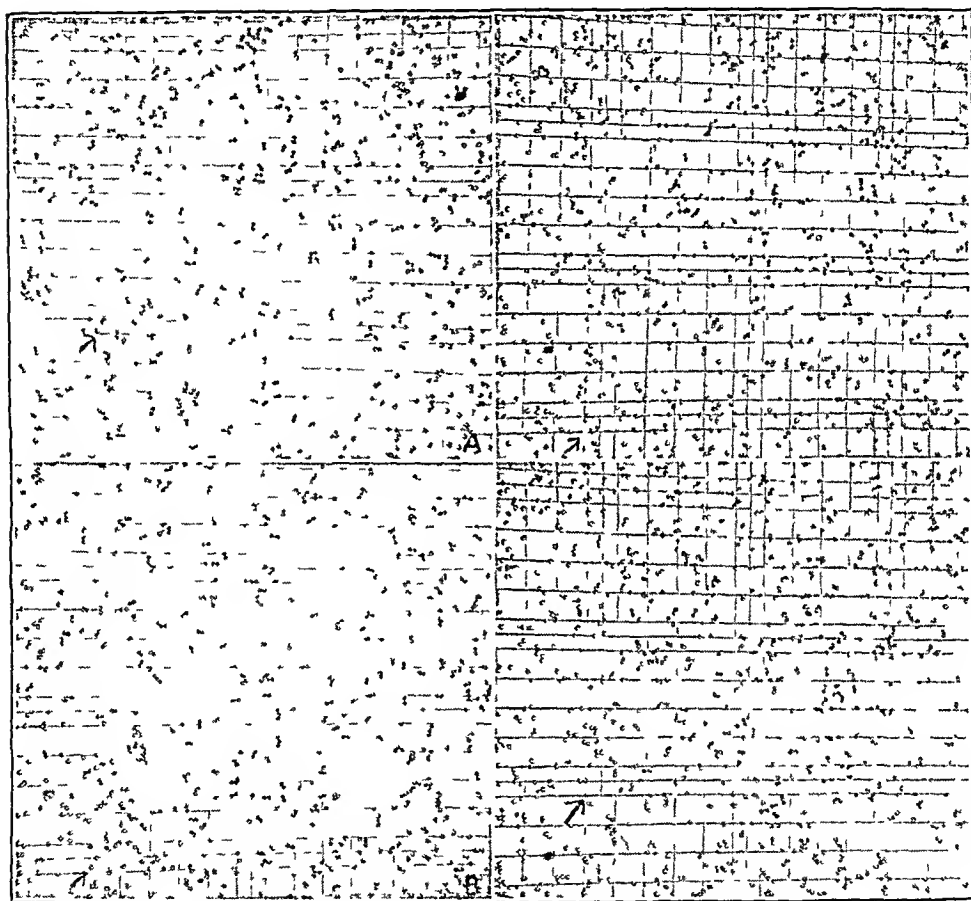
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\* From the Laboratory of Clinical Chemistry Presbyterian Hospital The work here reported is part of a study on arthritis by Dr Ralph Pemberton of Philadelphia, in collaboration with Dr Robert B Osgood of Boston The expenses of the investigation were defrayed by contributions from various sources including a number of patients

<sup>1</sup> Peirce E G and Pemberton Ralph Arch Int Med **39** 421 (March) 1927

<sup>2</sup> Rezinkoll P J Exper Med **38** 441 (Oct) 1923

method<sup>3</sup> was used and the color intensified by the addition of acetone. Two hundredths cubic centimeters of blood was used as a minimum. Several "first" drops were required to yield even this amount. The quantity of iron present in so small an amount of blood was too minute for accurate analysis, and the results were eventually abandoned as unreliable. Attempts were then made to determine variations in the concentration of hemoglobin in the different specimens of blood by the amount of dilution necessary to render invisible the characteristic



Photomicrographs of the red cell count of first (upper row) and freely flowing (lower row) drops of finger blood (case, Brown). The arrows indicate the four large squares counted on each plate. The two upper plates (eight large squares) of the first drop (*A*) give a count of 4,584,000 red blood cells, the two lower plates of the freely flowing drop (*B*) give a count of 5,040,000 red blood cells.

absorption spectra of oxyhemoglobin. These were not successful because the point of disappearance of the absorption bands was too indefinite.

It was finally decided to carry through the whole technic for blood counting described by Peirce and Pemberton, with this difference after

<sup>3</sup> Brown, A. L. *J. Am. Chem. Soc.* **44**: 423 (Feb.) 1922.

the counting chamber was filled, it was placed under the low power of a microscope equipped with a euscope and plate holder, and the spread was photographed. This provided a permanent record of the blood spread which could then be counted at leisure by more than one worker, thus avoiding the personal equation in the actual counting. Two photomicrographs were made of each spread, one of each side of the dividing moat of the counting chamber. In figure 1 are reproduced the photo-

TABLE 1—*Red Cell Counts of First and Freely Flowing Drops of Blood from Finger of Patients with Arthritis and of Normal Subjects*

Patient	Patients with Arthritis				Remarks
	1925 Date,	Drop First	Flowing Freely	Difference	
Vorhees	10/ 5	4,730,000	4,284,000	+446,000	Severe
Cro-ter	10/12	4,844,000	4,336,000	+508,000	Mild
Silverman	10/13	5,124,000	5,206,000	— 82,000	Severe
Bubb	10/14	4,668,000	4,490,000	+178,000	Mild (cured)
Davis	10/15	4,912,000	5,480,000	—568,000	Severe
Blab-n	10/17	4,958,000	5,150,000	—192,000	Severe
Norton	10/23	4,442,000	4,656,000	—214,000	Severe
Boyle	10/23	5,324,000	5,534,000	—210,000	Mild
Harvey	10/26	4,146,000	4,354,000	—208,000	Mild
Brown	10/26	4,584,000	5,040,000	—456,000	Mild
Thompson	10/27	5,072,000	5,150,000	— 78,000	Severe
Stein	10/27	4,474,000	4,824,000	—350,000	Severe
Weye	10/28	4,734,000	4,240,000	+494,000	Mild
Evans	10/29	5,076,000	4,926,000	+150,000	Severe
Porter	10/29	5,470,000	5,740,000	—270,000	Severe
Lamey	10/30	5,878,000	5,154,000	+724,000	Severe
Lowry	10/30	3,914,000	4,234,000	—320,000	Severe
Sch-ler	10/31	4,812,000	4,896,000	— 84,000	Severe
Medford	11/ 2	4,744,000	5,092,000	—348,000	Mild
McKeen	10/20	4,210,000	4,324,000	—114,000	Severe
Frederick	11/ 3	4,606,000	4,284,000	+322,000	Severe
Owens	11/ 3	4,718,000	4,344,000	+374,000	Severe
Mattson	11/ 4	4,398,000	4,688,000	—290,000	Severe
Gilmore	11/ 5	4,968,000	5,220,000	—252,000	Mild
Pic-rd	11/10	5,588,000	5,704,000	—116,000	Mild
Rowe	11/18	5,020,000	5,072,000	— 52,000	Severe
Davis	11/20	5,078,000	5,166,000	— 88,000	Severe
Chapin	11/20	4,870,000	4,410,000	+460,000	Severe
Stokes	11/23	4,752,000	5,384,000	—632,000	Severe
Normal Persons					
Ol-rk	10/27	4,628,000	4,308,000	+320,000	
P-kle	11/ 2	4,612,000	4,802,000	—190,000	
Thed-eh	11/ 3	4,744,000	4,738,000	+ 6,000	
Rei-t-r	11/ 5	5,152,000	4,770,000	+382,000	
How-ll	11/ 5	5,040,000	4,914,000	+126,000	
Mm-n	11/ 6	6,784,000	5,196,000	+1,588,000	
L-ph-m	11/ 6	6,480,000	5,570,000	+910,000	
L-d-ll	11/ 7	4,696,000	4,424,000	+272,000	
Dick-ns-n	11/ 9	6,060,000	5,914,000	+146,000	
Vorh-s	11/ 9	5,366,000	5,374,000	— 8,000	
Lew-s	11/ 9	6,032,000	6,214,000	—182,000	
F-st-r	11/10	5,962,000	5,332,000	+630,000	
Ev-ns	11/10	4,558,000	4,584,000	— 26,000	
Dav-s	11/11	4,772,000	4,980,000	—208,000	
Qu-nn	11/11	4,596,000	4,730,000	—134,000	
F-ck-si-n	11/12	4,754,000	4,526,000	+228,000	
Shell-b-gr	11/12	4,770,000	4,420,000	+350,000	
Sh-ble	11/12	4,558,000	4,656,000	— 98,000	
H-ppe	11/13	5,090,000	5,072,000	+ 18,000	
P-lm-r	11/13	5,020,000	5,052,000	— 32,000	
K-ngst-n	11/16	4,773,000	4,354,000	+419,000	
S-ng-rm-n	11/16	4,314,000	4,784,000	—470,000	
Vorh-s	11/18	5,172,000	5,176,000	— 4,000	
Sh-ble	11/24	4,642,000	4,586,000	+ 56,000	
Sm-th	11/27	4,396,000	4,210,000	+186,000	
DeV-lb-s	11/27	4,232,000	4,502,000	—270,000	
Lew-s	11/30	5,958,000	5,970,000	+ 12,000	
Qu-nn	11/17	4,390,000	4,474,000	— 84,000	

micrographs of spreads of the first and freely flowing drops from a case of arthritis that showed the typical "minus first drop" (case, Brown) After developing and drying, the negatives were placed over a source of illumination, and the cells were counted in the usual manner with the aid of a hand lens It was found best to count four of the six central large squares rather than the corner squares, as it was impossible to obtain an even focus over the whole field Each negative was counted by two persons working independently

The results of twenty-nine red cell counts obtained by this photographic method on a group of twenty-eight patients with arthritis and twenty-eight counts on twenty-four normal subjects are given in table 1 Of the patients with arthritis, fifteen, or 52 per cent, showed a "minus first drop," 31 per cent had a higher red cell content in the first drop than in the freely flowing blood, and there was no change, that is, the counts differed by less than 100,000 cells, in 17 per cent Of the twenty-eight observations on normal subjects, only six, or 21 per cent, had a minus first drop in contrast to the 52 per cent observed in the arthritic group Forty-three per cent of the normal persons had a higher count in the first drop of blood, and in 36 per cent there was no significant difference between the two specimens of blood

Forty-seven per cent of the nineteen patients with severe arthritis showed a "minus first drop," and 66 per cent of the nine patients with mild arthritis had a minus first drop These results, when compared with those obtained by Peice and Pemberton, among the arthritic group as a whole, show a somewhat larger percentage of cases in which the red cell count in the first drop of blood was lower than in the freely flowing blood A greater incidence of "minus first drop" was found among patients with mild arthritis and supposedly normal persons than was found in the previous series The contrast between the normal person and the patient with arthritis is, however, clearly shown

When an average was taken of the two series, thirty-nine patients with arthritis, or 44 per cent, showed a definite "minus first drop" in contrast to seven, or 14 per cent, of the normal persons who had a "minus first drop" or lower red cell count in the first drop of blood

#### CONCLUSION

The conclusions of Peice and Pemberton are in general confirmed in the present series In normal persons the red cell count of the first drop of finger blood was frequently (43 per cent) higher than the count of the freely flowing blood The majority of patients with arthritis showed the opposite condition and had a lower count in the first drop of finger blood than in the freely flowing blood

We wish to express our thanks to Dr John Eiman Director of the Pathological Laboratory of the Presbyterian Hospital, for his aid in the photographic work

# SPASTIC ESOPHAGUS AND MUCOUS COLITIS

ETIOLOGY AND TREATMENT BY PROGRESSIVE RELAXATION \*

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The cause and treatment of mucous colitis are among the outstanding problems of medicine today. This disorder, in common with esophageal spasm, involves hypertonus of smooth muscle of a portion of the alimentary tract and therefore both conditions will be reported in the present introductory study of their physiology. In parts of this article alimentary spasm in general will be considered.

The innervation of the alimentary tract in mammals and in man is not yet a closed question. In conflict with theories of "vagotonia" and "sympatheticotonia," certain recent studies emphasize that under varying conditions the vagi as well as the splanchnics, have both motor and inhibitory effects on the lower part of the esophagus, cardia, stomach and small intestine.<sup>1</sup> The striated muscle of the esophagus probably receives only motor fibers from the vagus.<sup>2</sup> The colon is supplied from the mesenteric plexuses, the pelvic plexus and the pelvic nerve,<sup>3</sup> but it is now denied that the vagus reaches this organ.<sup>4</sup>

It is generally admitted that the plexuses of Meissner and Auerbach control and coordinate peristalsis, but there has been considerable controversy as to what the muscle tissue itself can do when the nerve elements are stripped away.<sup>5</sup>

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\* From the Hull Physiological Laboratory, University of Chicago.

\* Read before the Section on Gastro-Enterology and Proctology at the Seventy-Seventh Annual Session of the American Medical Association, Dallas, Texas, April, 1926.

1 Carlson, A. J., Boyd, T. E., and Percy, J. F. Studies on Visceral Sensory Nervous System, *Arch Int Med* **30** 409-433 (Oct.) 1922. Bayliss and Starling. *J Physiol* **24** 99 (May) 1899, they found both kinds of fibers in the vagus supply to the small intestines, but only inhibitory in the splanchnics, while various investigators, also Boehm (*Arch f exper Path u Pharmacol* **72** 5, 1913) and Carlson (personal communication to the author) find both kinds in both vagus and splanchnics. Doubtless the effect of the splanchnics on the small intestine is mainly inhibitory. May. *J Physiol* **31** 260 (June 30) 1904. Katz and Winkler. *Beitr z exper Path* **85**, 1902. King, C. E. *Am J Physiol* **70** 183 (Sept.) 1924.

2 Carlson, A. J., Boyd, T. E., and Percy, J. F. *Am J Physiol* **61** 27 (June) 1922.

3 Langley and Anderson. *J Physiol* **18** 67, 1895. Elliott and Smith, Barclay. *J Physiol* **31** 272, 1904.

4 Carlson, in experiments on the severed colon, to be published. Boehm (footnote 1, third reference).

5 Bayliss and Starling (footnote 1, second reference). Alvarez, W. C. *The Mechanics of the Digestive Tract*, New York, 1922, p. 10. Carey, E. B. *Internat J Gastro-Enterol* **1**, July, 1921.

## ETIOLOGY OF ALIMENTARY SPASM

What is the cause of mucous colitis and spastic esophagus? Does the hypertonus originate in the mucous membrane, in the nerve endings, in the intramuscular plexus, in impulses from the extrinsic nerves, in increased excitations from the motor ganglions or nerve centers, in decreased excitations from inhibitory centers, or from a mixed source? A survey of the clinical literature fails to enable us to decide among these possibilities. We may begin with spasm of the lowermost portion of the esophagus, which often but perhaps not always occurs with spasm elsewhere in the esophagus. Vinson writes of cardiospasm "The etiology of the condition is unknown, the numerous hypotheses failing to explain all cases." Among other causes he mentions irritative lesions in the vagus nerves, esophagitis, fissures at the cardia, kinking of the esophagus at the hiatus esophagi and extrinsic pressure from the liver, and he recalls the hypothesis of foreign protein sensitivity.<sup>6</sup> Observers generally admit that many and various local irritations or lesions of the gastro-intestinal tract, such as appendicitis, cholecystitis, ulcers, varicosities and tumors, may produce spasm reflexly, either in the esophagus or colon or elsewhere. These conditions, it would seem, are due to excessive afferent stimulation. Among other causes of intestinal spasm are mentioned arteriosclerosis, uremia, lead poisoning and tabes. We know that alimentary spasm can readily be excited by various simple physiologic stimuli to the mucosa.<sup>7</sup> We know also that once mucous colitis has been incited with an inflamed mucosa and irritated nerve endings, food and other stimuli normally harmless will tend to maintain spasm. But we do not know whether the mucosa changes are primary and the spasm secondary or vice versa. Steindl points out that experimental pathologic and clinical observations make it seem probable that cardiospasm (excepting the reflex types) is due in mild cases to vagus neurosis, in severe cases to degenerative changes of the vagus.<sup>8</sup> He reminds us of the work of Exner, Heyrovsky, Paltauf and Kraus as indicating that spasm of the esophagus and colon occur as the result of excess activity of the vagus due to perivascular and degenerative changes in the vegetative nervous centers. He cites two cases of spastic ileus in which necropsy revealed lesions in

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6 Vinson, P. P. Diagnosis and Treatment of Cardiospasm, *J. A. M. A.* **82** 859-861 (March 15) 1924.

7 Cardiospasm may be induced by stimulation of the ninth and tenth nerve afferents, as by cold water in the esophagus or by carbonated water in the esophagus or stomach or by mechanical or chemical irritation of the mucosa in the cardiac region. Kronecker and Meltzer *Arch. f. Physiol.* 1883 supplement B, p. 355. Von Mikulicz *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **12** 569 1903.

8 Steindl, H. *Wien. klin. Wchschr.* (suppl.) **37** 3 (Oct. 30) 1924. Chronic progressive atrophy of the nerves was found with disappearance of the medullary sheaths and increase of interstitial connective tissue. Most of these patients he states, show clinical signs of vagotonia.

the centers of the vegetative neurons, that is, in the reticular substance of the medulla. Steindl concludes that enterospasm may have a demonstrable pathology in the vegetative nervous system and that disturbances of balance in the entire nervous system, organic or functional, may be in close connection with the occurrence of spasm. His conclusions may require some degree of revision when the distribution and effects of the vagus in man come to be definitely established.

It is beyond the scope of the present article to enter into a full account of present day knowledge of etiology or of treatment. Steindl points to the extrinsic, efferent nerves as common causes of spasm, and I shall try to give evidence which (to this extent) harmonizes with his conclusions,<sup>9</sup> but from an entirely new point of view.

It is commonly agreed that the nervous system has much to do with the initiation of mucous colitis, spastic colon and esophageal spasm but too often this is just a loose, general impression, and lacks confirmation by direct laboratory experiment. The functional nervous aspects of internal medicine as a rule are left to general speculation, and the internist may be impatient with the more detailed yet safer methods of laboratory investigation in this field.

#### RECENT EXPERIMENTS

Experiments were recently performed by me at the University of Chicago with a balloon in the spastic esophagus. In this way a record was obtained on smoked paper of the tonus of that muscle. It was found that under these conditions the muscles of the esophagus contracted strongly in the presence of emotion, but markedly also with every thought process that came to the subject. The esophagus ceased to contract as the nervous system quieted down, but only relaxed completely when the mental activity of the subject was made to cease by special methods.<sup>10</sup> This, then, is evidence of the connection between mental activity and at least some types of alimentary spasm.<sup>11</sup> In certain other experiments I found evidence of a relationship between mental activity and contraction of striated muscles, for it was shown that with complete relaxation of skeletal muscles, mental activity dwindles or ceases.<sup>12</sup>

9 Steindl follows Meltzer's theory of the origin of cardiospasm from disturbance of vagus fibers, while Rosenheim suggests that the inflamed mucosa causes the onset. The present observations do not rule out either of these two views in toto, but they bring out the rôle of a third factor, general nervous hyperactivity. Thomas and Kuntz report recent observations with nicotine showing the important influence of the extrinsic nerves on intestinal tonus. *Am J Physiol* **76** 606 (May) 1926.

10 Jacobson, Edmund. Voluntary Relaxation of the Esophagus, *Am J Physiol* **72** 387 (May) 1925.

11 Carlson, A. J., and Luckhart, A. B. *Am J Physiol* **57** 299 (Sept) 1921.

12 Jacobson, Edmund. Progressive Relaxation, *Am J Psychol* **36** 73-87 (Jan) 1925.

The method to produce an extreme degree of neuromuscular relaxation, as used in these experiments, I have recently described<sup>13</sup> This method has been found effective in the therapy of certain nervous conditions<sup>14</sup> It has been shown that by this method both the striated and the smooth muscles of the esophagus can be relaxed<sup>10</sup> This method can be tested also by the knee reflex As every clinician knows, the knee jerk is increased in what is commonly called relaxation, but Carlson and I investigated the influence of extreme relaxation produced by this method on the normal knee jerk and found that with advanced relaxation the jerk dwindles or disappears<sup>15</sup> I wish briefly to refer to three further sets of experiments which give evidence that the method of progressive relaxation reduces the activity and irritability of the nervous system In 1911, at Cornell University I found that the cerebral activity of attention apparently diminished in the presence of general relaxation<sup>16</sup> In extreme instances, advancing relaxation brought on a natural sleep even while the subject was sitting up awaiting his task In 1908, at Harvard I found that general nervous irritability, as measured on smoked records of the nervous start, diminishes with advancing relaxation<sup>18</sup> These experiments have recently been confirmed with the flexion reflex and carried further by Miller working under my direction at the University of Chicago<sup>19</sup>

#### CLINICAL OBSERVATIONS AND TREATMENT

I wish now to present in an introductory way some clinical observations which suggest that alimentary hypertension may be reduced by the method of progressive relaxation The clinical observations on the colon will need to be followed by corresponding laboratory investigations, and we should not consider the subject closed until then Only an abridged account of methods and a few sample records can be given in limited space Three cases are cited of esophageal spasm These are of the mild type without dilatation The diagnosis rested on the clinical symptoms and on the fluoroscopic observations Certain roentgen-

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13 Jacobson, Edmund The Technic of Progressive Relaxation, *J Nerv & Ment Dis* **60** 560-578 (Dec) 1924

14 Jacobson, Edmund Use of Relaxation in Hypertensive States, *New York M J* **111** 419 (March 6) 1920, Reduction of Nervous Irritability and Excitement by Progressive Relaxation, *J Nerv & Ment Dis* **53** 282 (April) 1921, Treatment of Nervous Irritability and Excitement, *Illinois M J* **39** 243 (March) 1921

15 Jacobson, Edmund, and Carlson, A J The Influence of Relaxation upon the Knee-Jerk, *Am J Physiol* **73** 324 (July) 1925

16 Jacobson, Edmund Further Experiments on the Inhibition of Sensations, *Am J Psychol* **23** 345-369, 1912

18 Jacobson, Edmund The Response to a Sudden Unexpected Stimulus, *J Exper Psychol* **9** 19 (Feb) 1926

19 Miller, M Changes in the Response to Electric Shock Produced by Varying Muscular Conditions, *J Exper Psychol* **9** 26 (Feb) 1926

ograms have been published <sup>20</sup> previously. In the first case the patient complained of epigastric pain radiating up under the sternum. Graphic records were made with a balloon in the spastic esophagus. A separate record was kept of the times when the patient complained of pain. It was found that these times corresponded with the presence of spasm in the esophagus. As the patient relaxed progressively during the course of a single hour the pain disappeared. This was not suggestion, for the patient could not see the record and therefore could not know when his esophagus was spastic. After he had received partial training, the pain present at the beginning of an experimental period disappeared as he became generally relaxed toward the end. As he became trained to habitual relaxation in the course of weeks or months, the subjective symptoms diminished or disappeared, and the roentgen-ray examination repeatedly revealed no spasm. It seems, therefore, safe to conclude that esophageal spasm, at least of mild degree, may be effectively treated by the present method.

CASE 1—H. K., a university student, aged 19, was first seen in January, 1923, when he complained of daily severe pain in the epigastrium, continuous for hours. There had been a sudden onset in 1920, marked by continuous cramping pain for five days, then partial relief, but for two weeks pain was so severe when he began to eat that he could scarcely continue. Since the onset, pain had been present daily, sometimes cramping, sometimes burning, sometimes relieved for an hour or more on eating. The pain sometimes seemed to merge into a vague type of distress which he said he could not distinguish from the feeling of fright he had when under nervous strain, such as during recitation at school or when present in large gatherings. He had been examined by an internist in 1920, and I am permitted to quote the observations. On examination nothing of note was found except a little epigastric tenderness. The roentgen-ray report was negative except for a slight irregularity of the bulb, a little duodenal stasis and a somewhat persistent "fleck." Motor meals and fractional examination gave some figures that were high. The feces, blood, urine and Wassermann examinations were negative. The patient was given a milk and cream diet and periodic alkalis, but the symptoms continued. In 1922, a neurologist had applied suggestive treatment to him with general discussion but the pain had continued. General physical examination which I made in 1923, including a proctoscopic examination, disclosed nothing new. A detailed study was therefore made with the fluoroscope, and esophageal spasm was plainly revealed as the source of the pain. This examination was clearly confirmed with graphic records at the University of Chicago, which have been published previously. These records, which were made with a balloon in the esophagus, showed that the presence of pain coincided with the presence of spasm. Spasm was also revealed in the roentgen-ray study of the pylorus and colon, and it is therefore possible that some of the pain proceeded from this source. The duodenal fleck was again seen. An Ewald meal yielded 370 cc., total acidity 60, free hydrochloric acid 52, combined hydrochloric acid 4, combined acids and salts 56, organic acid and salts 4, with a slightly positive Weber and benzidine test. Duodenal aspiration and stools were negative. The history of onset along with the finding of hyperacidity and the duodenal "fleck" with a little local tenderness suggest that duodenal ulcer may have been present, but this remains in doubt (1926).

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<sup>20</sup> Jacobson (footnote 10), *Physiology of Globus Hystericus*, J. A. M. A. 83: 911-913 (Sept 20) 1924.

Progressive relaxation was begun, Jan 8, 1923, with triweekly treatments but with daily practice on the part of the patient. Objective tests were made as this patient learned to relax. It was found with graphic records and with roentgenologic studies, as previously published, that this patient could voluntarily relax the esophagus. After many months of training, the knee-jerk test often showed a somewhat diminished reaction during relaxation.

Directions were given to the patient to alter his habits of life so as to avoid undue nervous strain. These directions, according to the patient's own admission, were not always followed. His progress was gradual and with brief relapses. His general appearance showed a change as he learned to relax, for pallor, shifting eye and anxious expression gave way to a better color, and a general air of determination. His reports show the gradual character of improvement on the subjective side. He reported slight improvement on the twelfth day, distinct improvement on the seventeenth. After five weeks he reported much improvement in pain for ten days, but this was followed by a relapse. At times when his personal affairs involved strain, such as college examinations, there was a tendency to relapse. After about six months he reported that pain was reduced to perhaps half the original duration or strength. It was found possible, for experimental purposes, to reinduce spasm and pain by putting the subject to certain tasks and strain.

At present, fluoroscopic tests no longer reveal spasm. The patient complains of an occasional pain, but it is very mild and infrequent in comparison with the original.

Four cases of mucous colitis are cited, other patients still being under treatment. The diagnosis here rests on the history, perhaps the palpation of a tender and firm colon, the presence of mucus, sometimes with ribbon-like or ball stools, the evidence of proctoscopy, and roentgen-ray examination. The barium enema, in connection with the roentgen ray, may give certain evidence of spasticity, but I have preferred to use the ordinary barium meal as a more normal test. I have taken as roentgen-ray evidence of colonic spasticity the presence of an irregularly narrowed colon, or the marked deepening of haustra.<sup>21</sup> The treatment of these colonic cases has generally taken more than a year. The patient continues to practice daily after being discharged by the physician. In judging the results, reliance has been placed not on the subjective reports of patients but on the objective observations. Mucus has practically disappeared or its occurrence has become infrequent and smaller in amount, the stool has lost its ribbon-like character and assumes a normal contour, the colon no longer is found firm and tender on palpation, the roentgen ray finally reveals a colon of normal markings.

CASE 2—E. T., a woman, aged 58, of a notable Irish family, complained in January, 1922, of symptoms of mucous colitis for thirty years. Her attacks formerly had come on about six times a year, but during recent years were on the increase, until of late they appeared two or three times a month. They were increasing in severity, for pain had been marked during the last four years all

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21 A brief account of the roentgen-ray signs of spasticity of the colon will be found in Carman, R. D. *Roentgen Diagnosis of Diseases of the Alimentary Canal*, ed 2, Philadelphia, 1921, pp 595 and 529. Also in Heagey, F. W. *J. Radiol.* 5:261 (Aug.) 1924, and Case, J. T. *New York State J. Med.* 21:158 (May) 1921. Analogous signs for the small intestine are given by Mills, R. W. *Am. J. Roentgenol.* 9:199 (April) 1922.

over the abdomen, sometimes shooting down the thighs, sometimes passing with a burning sensation up under the sternum. These attacks generally lasted about two days continuously, including the nights, and were relieved only by the electric pad and slightly by baking soda. Cramping abdominal pain occurred with bowel movement and epigastric distress usually followed eating or drinking within five to ten minutes. This pain generally disappeared spontaneously an hour or two after eating. In addition to mucus, she asserted that her stools had seemed to contain blood and pus. She emphasized her general weakness and inability to engage in normal activities. Her other complaints were constipation, frequent urination and pain in the chest sometimes with shortness of breath. Her husband was living and well. One son of 31 was mentally subnormal. She had had one



Fig 1 (case 2)—Feb 9, 1922, original examination in mucous colitis showed a highly spastic colon, with almost stricture-like appearance near splenic flexure, this filled out with a barium enema

stillbirth at seven months and another premature delivery at seven months, with death soon after birth. A boy had died at 5 months apparently from stomach trouble. The patient's past history was negative except that she had had a hemorrhoidectomy twenty-five years before and two operations on the uterus.

Physical examination revealed a short, stocky woman with good color, normal pulse and temperature, but with marked signs of suffering when seen during a spell. The heart and lungs were normal, as well as the other regions not mentioned here. The blood pressure was 188 systolic and 100 diastolic. Equisite tenderness was present over the gallbladder, and at McBurney's point, less marked over the colon generally. The entire colon was palpably firm, and there was slight abdominal resistance. The roentgen ray revealed a spastic colon (fig 1) with an area

of marked constriction near the splenic flexure. Under the roentgen ray, tenderness was severe over the gallbladder area and near McBurney's point, but marked also over the hepatic flexure and duodenum. Rather noteworthy hypermotility was shown by the barium reaching the descending colon in five hours. The duodenum showed stasis and limited motility, and the cecum also was not perfectly free. There were several fairly large hemorrhoids, and the proctoscope revealed some redness of the mucosa and on the right side beginning about 4 cm from the anal orifice. The vagina was narrowed following perineorrhaphy, and the cervix had been partially amputated. The stools were yellow or greenish, with considerable mucus. The hemoglobin content was 80 per cent. The blood was otherwise negative, including the Wassermann reaction. An Ewald meal gave no evidence

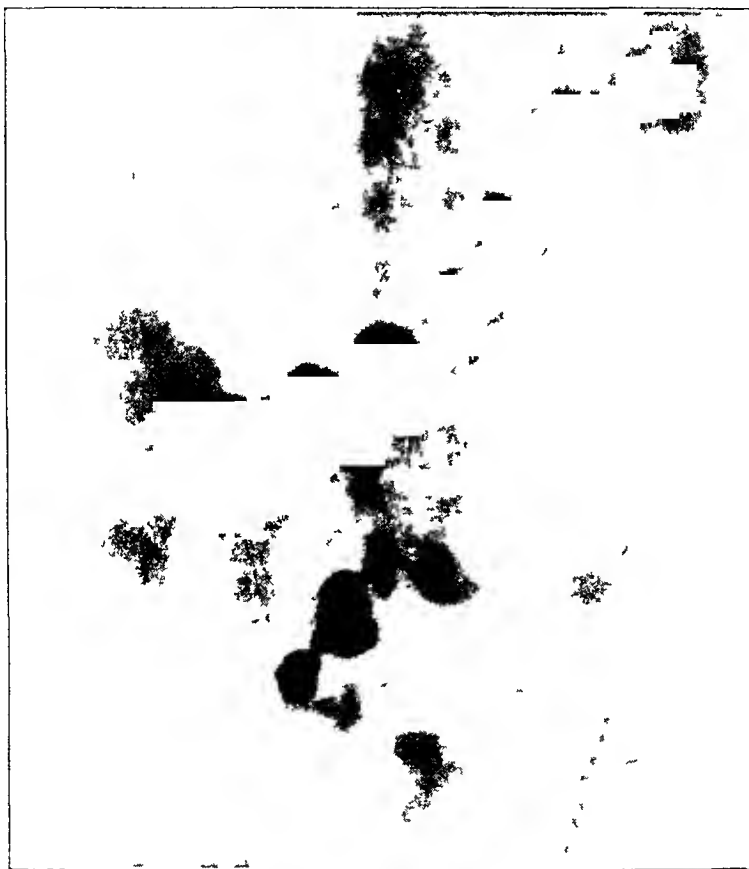


Fig 2 (case 2) —May 12, 1925, the colon much improved but still somewhat spastic on twenty-four hour observation. The constricted band near the splenic flexure was now filled out. Later observation (forty-eight hours) showed stasis.

that was noteworthy, nor a stool culture. Aspiration of the duodenum showed the presence of strings of mucus, pus and squamous epithelial cells in the fraction presumed to be from the gallbladder. Ferments were normally present. A cystoscopic examination made by a consultant showed a chronic trigonal hyperemia, which was treated with applications of silver nitrate.

When treatment was begun with this patient, it did not occur to me to try progressive relaxation, and for about three months the more or less usual therapeutic measures were applied. Diet was carefully limited, liquid petrolatum was given by mouth and olive oil by retention enemas. Much daily rest in bed was prescribed in the ordinary way. But these and other accessory measures did not prove successful. Tincture of belladonna, benzyl benzoate even diathermy for pain

were tried and discarded. The failure of these measures, from which much had been hoped, incidentally gave evidence that the patient's condition did not respond to "suggestion." I considered the removal of the appendix and gallbladder, but a surgical consultant, Dr. E. Willys Andrews, seemed doubtful, and Dr. Edmund Andrews suggested that progressive relaxation be tried.

Treatment with progressive relaxation was accordingly begun in May, 1922. This patient was not very clever at learning to recognize muscular contractions, which is part of the present method. One of the striking features of her postural tonus was a severe frown with wrinkled forehead, and much practice was devoted to this region. As she gradually became relaxed, the hospital record of stool examinations showed a change. May 1-6, there were shreds of mucus, May 11-12,



Fig. 3 (case 3) — July 18, 1923, original examination of spastic colon in mucous colitis

small shreds, May 10-23, no mucus, then a reappearance, May 25. Thereafter mucus was largely absent. The general symptoms and signs gradually abated, except for a relapse during the last two weeks of July. Aug. 15, 1922, while still in the hospital the gallbladder region had become entirely free from tenderness, the ileocecal region showed but slight tenderness and the transverse colon but little. Pain on defecation was much diminished and often absent. Attacks of pain were now infrequent and no longer of former severity. The stools were usually normal. The patient was discharged from the hospital, but continued daily practice at home with practically no further direction from the physician.

At home she continued without further medical aid to improve at relaxing her muscles, just as an individual will improve with practice after instruction at the piano or dancing or other physical feat. After about six months more, tenderness

had disappeared from the abdomen, and the colon no longer was firm to palpation. She went to California and nursed her husband who had become ill, drove a motor car and performed other functions with impunity for the first time in many years. A roentgenogram (fig 2) was made for me in 1925 by Dr A B Smith at La Jolla, and reveals a colon no longer extremely spastic. Relapse with this patient has been mild, infrequent and brief.

CASE 3—E R, a married woman, aged 34, complained in June, 1923, of spells of diarrhea, often with mucus, for the preceding fourteen years. She mentioned occasional tenderness in the right side or umbilical pain. She had had a partial tonsillectomy in childhood, pneumonia and the usual other disorders. At 12 she had an enlarged thyroid, which was treated with roentgen rays until it subsided. Her mother also had colitis for several years.



Fig 4 (case 3) —Aug 22, 1924, diminished spasticity of colon after about one year of treatment

The present illness began at the age of 20, with much distress and diarrhea after meals. This seemed especially marked after nervous difficulties over love affairs. About a year later, a badly infected appendix was removed. Distress and diarrhea continued severe during the following few months, with moderate improvement thereafter. In 1914, there was occasional vomiting after or before meals. She was married in 1917. Spells of diarrhea seemed to come on after getting chilled, after eating an ordinary meal, after anxiety about her baby, or worry about a visit. After the first childbirth, 1919, her hemoglobin "sank to a very low figure." A second childbirth occurred in 1921. The perineum was lacerated, impairing control of the anal sphincter.

Examination disclosed a fairly nourished woman. The blood pressure was 116 systolic and 80 diastolic. The eyes, nasal passages and tongue were normal. The tonsil remnants occasionally showed a little dried streak or pus on the left. The thyroid was fairly firm but not enlarged. The heart was normal. The lungs

showed no signs of an active process. At the time of first examination the colon was not tender or palpable. A midline scar from the pubis to about 2 cm above the umbilicus dated from a cesarean section. The deep reflexes were of increased liveliness. Proctoscopic examination revealed a little generalized redness of the mucosa, beginning about 9 cm from the anus with a little mucus, but no inflammation of the cryptic region. The roentgen ray showed a spastic colon (fig 3). The urine was normal. Cultures of the feces gave *Bacillus coli* and *Staphylococcus albus*. No tubercle bacilli and no ova or parasites were found. A basal metabolic test, roentgenograms of the teeth and a Wassermann test of later date proved negative.

Treatment was begun with relaxation and restriction of diet to milk, eggs, stewed fruits, cereals, custards and jelly. Observations disclosed that spells of



Fig 5 (case 3) —Feb 16, 1926, improved condition of colon two years later

diarrhea occurred after what for her appeared to be dietary indiscretions, such as eating onions, after coryza, but most often after general overstrain, such as occurred when her husband or children fell ill. It took about forty-five days before she began to make apparent progress in relaxation. Diarrhea became markedly diminished at about this time. A recurrence followed the illness of her husband. Previous to treatment such spells had lasted from one week to a month, with a minimum of three to four days. During the first year of treatment the spells not only became less frequent but were generally stopped after intensive relaxation during many hours for one to three days. Roentgenograms taken in August, 1924, showed a colon not far from normal in appearance (fig 4). The pylorus did not open until after ten minutes. The patient reported marked improvement at this time, the spells coming about one fifth as often as formerly and lasting about one fifth as long. The great length of treatment seemed to be due to failure of the patient to follow directions about diminishing her domestic and

social activities. Instructions had to be repeated many times before they were followed. She continued to practice at home after this time, occasionally calling for treatment. At the end of this time spells had become infrequent. Roentgenograms now reveal a practically normal colon (fig 5), but a little pylorospasm has persisted.

At present, in comparison with the period before treatment, she shows a greatly diminished tendency toward spells. During prolonged intervals she is free from symptoms and signs. However, spells of relatively shorter duration than formerly still sometimes tend to appear after coryza or overwork. She has shown a certain flippancy in regard to cooperation and a consequent lack of skill at relaxation, which seems to account for the variations in her condition. Tonsillectomy has just been performed. The stability of result in this case does not equal that of the three others cited.

Any present day treatment of alimentary spasm will of course begin with a thorough search and removal, if possible, of focal infections. There is a tendency to relapse for a brief period if the patient is put under severe nervous strain, or on the onset of marked infection, such as severe coryza. In the present studies, other measures besides progressive relaxation were excluded so far as possible in order to isolate

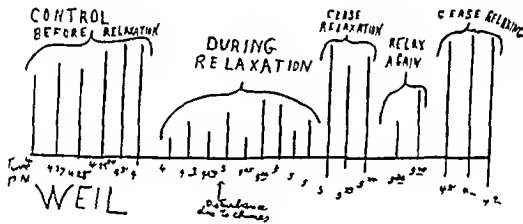


Fig 6 (case S W) —Test of ability to relax as shown by diminution of knee reflex in mucous colitis. This record shows fair but not extreme relaxation, which is marked by complete disappearance of the knee jerk.

the effects of this method alone. However, this could not always be accomplished perfectly. It seemed best, in order to favor the results, to advise the patient to masticate food thoroughly, and to avoid such foods as seemed to the patient and the physician to stir up colonic spells. At times when there was constipation, liquid petrolatum or an emulsion of liquid petrolatum and agar was used for a brief period, in two cases when the proctoscope showed an irritated mucosa, olive oil retention enemas were employed. However, such accessory measures have been in wide use heretofore and are well known to be uncertain in themselves to bring about good results in mucous colitis, therefore, it may be assumed that they play a minor rôle in the present studies. The effect of progressive relaxation was most clearly isolated with the first patient studied, for here months of treatment in bed at home and in the hospital with diet and other measures, including diathermy, had failed to produce the desired result, showing that the condition did not respond to ordinary rest or suggestion. It was only when she later learned to relax that the tenderness disappeared and the objective indications of spasticity waned.

Something more than what is popularly termed relaxation is meant in these reports. It has been found that to train an investigator in this field, as is done at the University of Chicago, requires months of preliminary training.

#### SUMMARY AND CONCLUSIONS

Laboratory investigations have given evidence that mental and emotional activity may take part in the production and maintenance of esophageal spasm, at least of the mild type. Other experiments have shown a relationship between mental activity and contraction of skeletal muscles, for with advancing muscular relaxation mental and emotional activity dwindle or cease. These experiments have led the way to the development of a method called progressive relaxation, which has been shown to diminish central nervous activity as tested by the flexion reflex and other reflexes. In practice this method is tested by the diminution of the knee reflex during advanced relaxation. It has been shown that by this method at least one type of alimentary spasm (esophagus) may be diminished in a number of persons. This method apparently acts through the reduction of reflexes of skeletal musculature, thereby bringing with it a corresponding reduction of proprioceptive impulses and of reflex stimulation of the alimentary tract. By this means, in all probability, the excitability of the nerve centers is reduced. Clinical observations now suggest that this method may be successfully applied to the treatment of mucous colitis.

# STUDIES ON PERITONITIS

## I PRODUCTION OF EXPERIMENTAL PERITONITIS AND SURVIVAL FOLLOWING INTRAPERITONEAL INJECTION OF *BACILLUS COLI*\*

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AND

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CLEVELAND

Attempts have been made to produce experimental peritonitis by the intraperitoneal injection of bacteria into rabbits (Wegner,<sup>1</sup> Benmans<sup>2</sup> and others) and into dogs (Noetzel<sup>3</sup>). The results have been conflicting, some investigators reporting rapid death, others, survival of the animals. The discrepancy is probably due to the variability in the numbers, type and pathogenicity of the organisms used as well as to the nature of the fluid employed in the suspension of the bacteria. Later work has shown that the intraperitoneal injection of relatively large quantities of broth cultures of virulent *Bacillus coli* will kill rabbits quickly without inducing severe peritoneal reaction (Steinberg and Ecker<sup>4</sup>). The same applies to guinea-pigs and to rats (unpublished experiments—Steinberg).

This study was undertaken to determine the conditions necessary for the production of fatal peritonitis in the dog by the intraperitoneal injection of bacteria.

### EXPERIMENTAL WORK

The micro-organism used in this investigation was a strain of virulent *B. coli* isolated from the blood of a human being. Dogs weighing from 15 to 20 Kg. were employed.

*Intraperitoneal Injection of B. coli Suspended in Saline Solution*—Seven dogs were used. In five of these the injection consisted of three agar slants of a twenty-four hour culture of *B. coli* suspended in 40 cc. of 0.9 per cent sodium chloride solution, and in two others it consisted of 5 agar slants of a similar culture in 75 cc. of saline.

One of the dogs that received three agar slants in 40 cc. of saline died in about fourteen hours, with severe hemorrhagic serofibrinous peritonitis.

The remaining six dogs were ill for the first three or four hours after the injection, but they survived.

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\* From the Department of Pathology, School of Medicine, Western Reserve University.

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1 Wegner, G. Arch. klin. Chir. **20** 51, 1876-1877.

2 Benmans, I. H. C. Brit. J. Exper. Path. **5** 123 (June) 1924.

3 Noetzel, W. Arch. klin. Chir. **57** 311, 1898.

4 Steinberg, B., and Ecker, E. E. J. Exper. Med. **43** 433 (April) 1926.

*Intraperitoneal Injection of Broth Culture of B coli*—Five dogs were employed. In three, the injection consisted of 50 cc and in two, of 100 cc of a twenty-four hour broth culture of *B coli*. The animals were ill for three or four hours after the injection, but all survived.

*Intraperitoneal Injection of B coli and Aleuronat*—Two dogs were used. Each received an injection of 50 cc of a twenty-four hour broth culture of *B coli* containing 5 Gm of aleuronat. The dogs were ill but survived.

*Intraperitoneal Injection of B coli and Gum Tragacanth*—Eight dogs were employed. In five, the injection consisted of 40 cc of a 25 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride solution containing 3 agar slants of a twenty-four hour culture of *B coli*. In three, the injection consisted of 40 cc of a 25 per cent suspension of gum tragacanth in a twenty-four hour broth culture of *B coli*. The eight animals died. All became ill in about one and one-half hours after the injection. They vomited, at first food, later bile-stained fluid. Rapid respiration and weakness were early symptoms. Severe diarrhea usually occurred in about four hours after the injection. Prostration and finally coma began about one-half to one hour before death, which occurred in from five to fourteen hours.

At autopsy, the peritoneal cavity contained from 100 to 250 cc of a bloody fluid, containing a few flakes of fibrin, and some of the tragacanth. Both visceral and parietal peritoneum were generally intensely hyperemic and hemorrhagic. The parenchymatous organs showed a moderate degree of cloudy swelling and congestion. Smears of peritoneal fluid showed numerous gram-negative bacilli, and cultures proved them to be pure *B coli*.

*Intraperitoneal Injection of B coli Suspended in Gum Tragacanth and Direct Drainage of the Thoracic Duct*—A glass cannula with rubber tubing attached was inserted directly into the thoracic duct of three dogs. The operation was performed under ether anesthesia and in each case lasted about twenty minutes. Eight hours after the operation, the animals were in excellent condition and received an intraperitoneal injection consisting of 40 cc of a 25 per cent gum tragacanth suspension in 0.9 per cent sodium chloride solution containing 3 agar slants of a twenty-four hour culture of *B coli*. They died in four and one-half, five and one-half and seven and one-half hours after the injection, respectively. Throughout the duration of the experiment there was a copious drainage of lymph in the three animals. After the intraperitoneal injection, these dogs showed the same signs and symptoms as three others which were not drained, but which received the same intraperitoneal injection. These signs and symptoms were described in the previous section. The autopsy observations were similar in drained and undrained animals, namely, a severe hemorrhagic serofibrinous peritonitis.

*Intraperitoneal Injection of Gum Tragacanth Alone*—As controls, three dogs received intraperitoneal injections with a 25 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride solution. The injection consisted of 40 cc of this suspension. The animals showed no symptoms, and all survived.

#### CONCLUSIONS

1 When large numbers of virulent *B coli* suspended in physiologic sodium chloride or broth cultures of *B coli* are injected intraperitoneally into dogs, the animals practically always survive.

2 Dogs also survive the intraperitoneal injection of broth cultures of *B coli* containing aleuronat.

3 When large numbers of virulent *B coli* suspended in gum tragacanth are injected intraperitoneally into dogs, the animals always die, and the outcome is not altered by direct drainage of the thoracic duct.

*Summary of Experiments*

Number of Dogs Used	Type and Quantity of Intraperitoneal Injection	Outcome and Remarks
	Saline Suspension of Bacteria	
5	3 agar slants of B coli in 40 cc of 0.9% sodium chloride solution	Four survived, one died
2	5 agar slants of B coli in 75 cc of 0.9% sodium chloride solution	Both survived
	Broth Culture of Bacteria	
3	50 cc of 24 hour culture of B coli in broth	All survived
2	100 cc of similar culture	Both survived
	Broth Culture of Bacteria and Aleuronat	
2	50 cc of 24 hour broth culture of B coli plus 5 Gm of aleuronat	Both survived
	Gum Tragacanth alone	
3	40 cc of 2.5% gum tragacanth suspension in 0.9% sodium chloride solution	All survived
	Suspension of Bacteria in Gum Tragacanth	
5	40 cc of 2.5% gum tragacanth suspension in saline containing 3 agar slants of a 24 hour culture of B coli	All died
3	40 cc of a similar suspension	Thoracic duct drained, all died
	Broth Culture of Bacteria plus Gum Tragacanth	
3	40 cc of a 2.5% suspension of gum tragacanth in a 24 hour broth culture of B coli	All died

# STUDIES ON PERITONITIS

## II PASSAGE OF BACTERIA FROM THE PERITONEAL CAVITY INTO LYMPH AND BLOOD<sup>+</sup>

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AND

HARRY GOLDBLATT, M D

CLEVELAND

It has been shown in a previous paper that dogs survive intraperitoneal injections of colon bacilli suspended in saline, but that they succumb to intraperitoneal injections of colon bacilli suspended in gum tragacanth. This study concerns itself with the fate of the bacteria after their intraperitoneal injection in the two suspensions mentioned.

Since the original investigations of von Recklinghausen,<sup>1</sup> 1863, much work has been done on the absorption from the peritoneal cavity of dyes (both diffusible and colloidal), organic and inorganic substances in solution and suspension, and colloids, including bacteria. The literature on the subject has been covered by Bolton,<sup>2</sup> 1921, Katsura<sup>3</sup> and Notkin.<sup>4</sup> The results of the various investigators have been conflicting in regard to the mode of absorption of the various substances. In the investigation of absorption by way of the lymphatics, the thoracic duct had been the only channel considered until the work of Bolton, 1921, and of Katsura 1924, indicated the importance of the right lymphatic duct.

### METHOD OF STUDY

Dogs were used for these experiments. In most instances the animals were fed the night before the experiment, but in some cases they fasted for twenty-four hours. Under ether anesthesia, and with aseptic precautions, a glass cannula was introduced into the thoracic duct and another into the femoral artery. All communications between thoracic duct and veins of the neck were ligated. The mode of communication between thoracic duct and veins is variable. Failure to recognize this variability may leave a connection between lymphatic and venous systems. Figure 1 illustrates diagrammatically some of the more common variations.

In the qualitative study, cultures of lymph were taken in broth and on Russell's double sugar, and cultures of blood were taken in broth only. After forty-eight hours, all broth cultures were transferred to Russell's medium, and

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<sup>+</sup> Aided in part by a grant from the American Medical Association.

<sup>†</sup> From Department of Pathology, School of Medicine, Western Reserve University.

<sup>†</sup> Fellow in Medicine, National Research Council.

1 Von Recklinghausen. *Virchow's Arch f path Anat* **24** 172, 1863.

2 Bolton, C. J. *J Path & Bact* **24** 429 (Oct) 1921.

3 Katsura, Shigehiro. *Tohoku J Exper Med* **5** 294, 1924.

4 Notkin, J. A. *Virchow's Arch f path Anat* **255** 471, 1925.

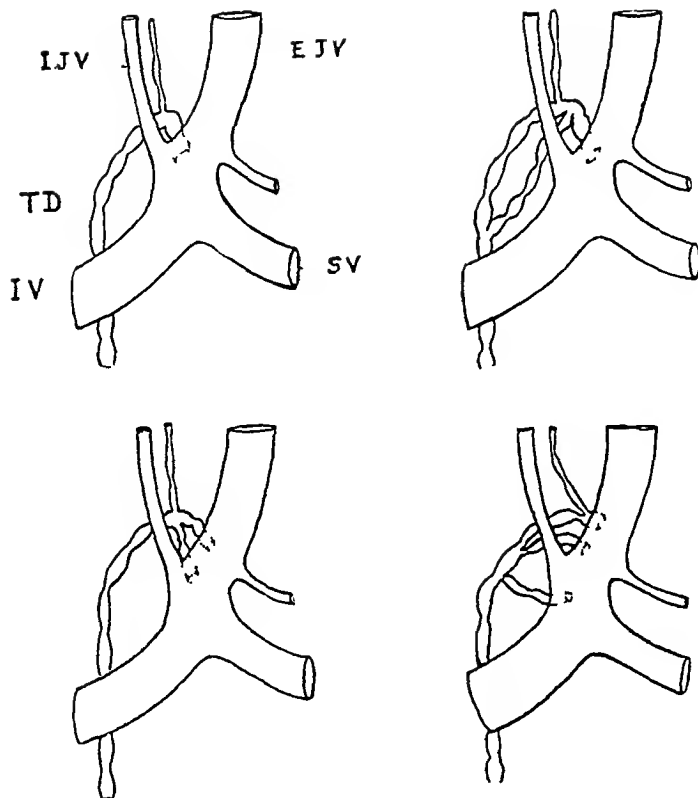
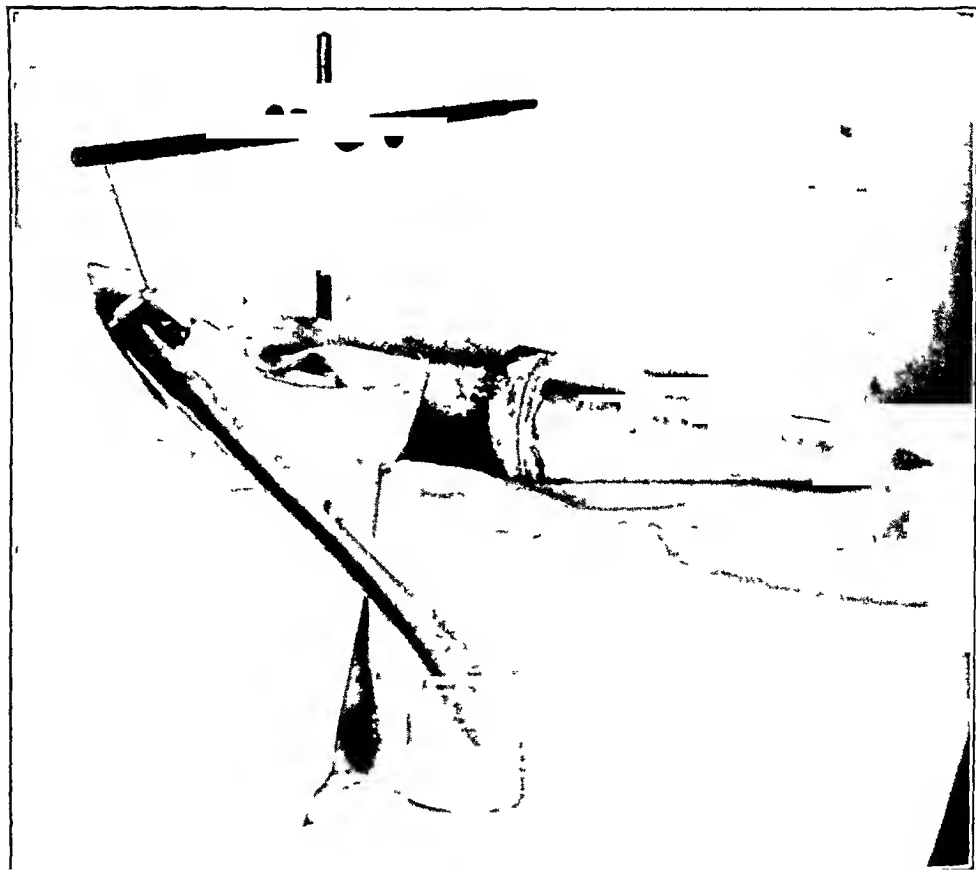


Fig 1—Diagram illustrating some of the variations of the communication between the thoracic duct and the veins of the neck *I J V* indicates internal jugular vein *E J V*, external jugular vein, *t d*, thoracic duct, *S V*, subclavian vein, *I I*, innominate vein



in from three to five days the broth cultures were tested by Ehrlich's method for the presence of indol

Immediately after the cannulas were inserted, several control cultures of lymph and blood were taken, then the intraperitoneal injection of bacterial suspension was made, and following this, lymph and blood were cultured simultaneously at frequent intervals

For the quantitative estimation of bacteria in lymph and blood, the plating method of Karsner, Brittingham and Richardson<sup>5</sup> was used

TABLE 1—A Typical Protocol of an Experiment Intraperitoneal Injection of *B. coli* Suspended in Saline<sup>5</sup>

Lymph Cultures (Thoracic Duct)				Blood Cultures (Femoral Artery)			
Time	Smear	Russell	Indol	Time	Smear	Russell	Indol
12 20	—	—	—	12 20	—	—	—
12 22	—	—	—	12 22	—	—	—
12 24	—	—	—	12 24	—	—	—
12 26½	B. coli from 3 agar slants in 40 cc of physiologic sodium chloride was injected intraperitoneally						
12 27	—	—	—	12 27	—	—	—
12 28	—	—	—	12 28	—	—	—
12 29	—	—	—	12 29	—	—	—
12 30	—	—	—	12 30	—	—	—
12 31	—	—	—	12 31	—	—	—
12 32	—	—	—	12 32	—	—	—
12 33	—	—	—	12 33	—	—	—
12 34	—	—	—	12 34	—	—	—
12 35	—	—	—	12 35	—	—	—
12 36	+	+	+	12 36	—	—	—
12 37	+	+	+	12 37	—	—	—
12 38	+	+	+	12 38	—	—	—
12 39	+	+	+	12 39	—	—	—
12 40	+	+	+	12 40	—	—	—
12 41	+	+	+	12 41	—	—	—
12 42	+	+	+	12 42	+	+	+
12 43	+	+	+	12 43	+	+	+
12 44	+	+	+	12 44	+	+	+
12 47	+	+	+	12 47	+	+	+
12 52	+	+	+	12 52	+	+	+
1 02	+	+	+	1 02	+	+	+
1 12	+	+	+	1 12	+	+	+
1 26½	+	+	+	1 26½	+	+	+

\* B. coli appeared in the thoracic duct lymph in nine and a half minutes and in blood in fifteen and a half minutes. Cultures were taken for one hour after the intraperitoneal injection

# I CULTURES OF BLOOD AND LYMPH AFTER INTRAPERITONEAL INJECTION OF B. COLI SUSPENDED IN SALINE SOLUTION

(a) *Qualitative*—Five dogs were used. The intraperitoneal injection consisted of 40 cc of 0.9 per cent sodium chloride solution containing three agar slants of a twenty-four hour culture of *B. coli*. Table 1 is a protocol of a typical experiment, table 2 is a summary of the five experiments.

The control cultures were negative. The bacteria appeared in lymph and blood, slightly earlier in lymph (table 2). In experiment 4, in which the time of the first appearance of bacteria in lymph and blood com-

<sup>5</sup> Karsner, H. T., Brittingham, H. H., and Richardson, M. L. J. M. Research 44:83 (Sept.) 1923.

cides (four minutes) these were the first cultures taken after the injection, and in experiment 5, in which the same thing occurs, the interval between cultures was five minutes

(b) *Quantitative*—To compare the number of bacteria which pass into lymph and blood after the intraperitoneal injection of saline suspension of *B coli* (40 cc of 0.9 per cent sodium chloride solution containing three agar slants of a twenty-four hour culture), the plating method of Karsner, Bittingham and Richardson<sup>5</sup> was used. Plates of Endo and Russell mediums were employed. Table 3 illustrates the results of the experiments.

TABLE 2—Intraperitoneal Injection of Colon Bacilli Suspended in Physiologic Sodium Chloride

No. of Experiment	Weight of Dog in Kg.	Time of First Appearance of Bacteria in		Duration of Experiment After the Injection
		Lymph (Thoracic Duct)	Blood (Femoral Artery)	
1	15	9 minutes	13 minutes	1 hour
2	20	11 minutes	12½ minutes	45 minutes
3	20	9½ minutes	15½ minutes	1 hour
4	17	4 minutes	4 minutes	2 hours
5*	18	24 minutes	24 minutes	3 hours
6	14	Thoracic duct intact	4 minutes	30 minutes

\* Dog placed in Fowler's position

TABLE 3—Bacterial Counts of Lymph and Blood After Intraperitoneal Injection of *B. Coli* Suspended in Saline

Experiment 1			Experiment 2		
Number of Minutes after Injection	Number of Bacteria per Cc		Number of Minutes after Injection	Number of Bacteria per Cc	
	Lymph	Blood		Lymph	Blood
6	58,000	Sterile	10	64,000	11,000
20	5,240,000	900	20	1,170,000	Not estimated
60	Not countable in dilutions made	360	40	800,000	11,000
			60	80,000	3,000
			95	4,000	860
			125	10,000	130
			135	20,000	60

In spite of the margin of error of the method employed, the difference between the number of bacteria in lymph and blood was so great that the results are of value.

Two dogs were used. In the first experiment, which was continued for only one hour, the bacteria appeared earlier, and in far greater numbers, in lymph than in blood. In the second experiment, which was continued for two hours and thirty-five minutes, the number of bacteria was again greater in lymph than in blood, but the difference was not so great as in the first experiment. This may be accounted for by the fact that the flow of lymph in the second dog was much greater than in the first. In the second experiment, after twenty minutes, there occurred a rapid diminution of the number of bacteria in lymph and in blood.

Control cultures taken prior to the intraperitoneal injection of the organisms were sterile

*Necropsy*—The animals used in experiments I *a* and in I *b* were killed in from two to ten hours after the injection. In those killed two hours after the injection, no gross abnormalities were found, and usually only a small amount of the injected material remained. In those killed later (up to ten hours after the injection) a slight amount of hyperemia of visceral and parietal peritoneum was usually seen.

## II CULTURES OF BLOOD AND LYMPH AFTER INTRAPERITONEAL INJECTION OF *B. COLI* SUSPENDED IN GUM TRAGACANTH

(a) *Qualitative*—Eight dogs were used. In five dogs (experiment 1 to 5, table 4), the injection consisted of three agar slants of a twenty-four hour culture of *B. coli* in a 2.5 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride solution.

TABLE 4—*Intraperitoneal Injection of Colon Bacilli Suspended in Gum Tragacanth*

No. of Experiment	Weight of Dog in Kg.	Time of First Appearance of Bacteria in		Duration of Experiment After the Injection
		Lymph (Thoracic Duct)	Blood (Femoral Artery)	
1	15	9 minutes	Sterile	2 hours
2	20	16 minutes	Sterile	2½ hours
3	18	14 minutes	Sterile	1 hour 20 min
4	19	19 minutes	Sterile	2 hours
5*	18	35½ minutes	Sterile	2 hours
6	18	Thoracic duct intact	Sterile	6 hours (until death)
7	13	Thoracic duct intact	Sterile	2 hours
8	14	Thoracic duct intact	Sterile	1 hour 40 min

\* Dog placed in Fowler's position

In these experiments bacteria appeared in lymph but not in blood, and in the lymph, they appeared later than in the experiments in which bacteria suspended in saline were injected. One animal (experiment 5, table 4) was placed in Fowler's position at the beginning of the experiment. There was an appreciable delay in the time of the first appearance of bacteria in lymph.

In three dogs (experiments 6, 7 and 8, chart 4), the thoracic duct was allowed to remain intact, in order to permit the passage of bacteria from the lymph into the blood, and blood cultures were taken. However, the blood was sterile. This can be explained, perhaps, by the bactericidal powers of the blood for the small number of organisms which entered by the way of the duct.

(b) *Quantitative*—Two experiments were performed. In one dog (experiment 1, table 5), the injection consisted of three agar slants of a

twenty-four hour culture of *B coli* in a 2.5 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride solution. The blood remained sterile throughout the experiment. Bacteria appeared in lymph but in much smaller numbers than in the experiments in which *B coli* suspended in saline were injected (table 3 and 5, experiment 1).

In another dog (experiment 2, table 5), the injection consisted of three agar slants of a twenty-four culture of *B coli* in a 4 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride solution. The blood remained sterile throughout the experiment, which lasted five hours. There was a delay in time in the first appearance of bacteria in the lymph. As in the first dog (experiment 1, table 5), the number of bacteria in lymph was small. After two hours the number decreased, and the last two cultures were sterile. Control cultures taken before the intraperitoneal injection of the organisms were sterile.

TABLE 5—*Bacterial Counts of Lymph and Blood After Intraperitoneal Injection of B. Coli Suspended in Gum Tragacanth*

Experiment 1			Experiment 2		
Number of Minutes after Injection	Number of Bacteria per Cc		Number of Minutes after Injection	Number of Bacteria per Cc	
	Lymph	Blood		Lymph	Blood
10	170	Sterile	5	Sterile	Sterile
21	380	Sterile	10	Sterile	Sterile
36	460	Sterile	20	Sterile	Sterile
			30	Sterile	Sterile
			40	Sterile	Sterile
			50	60	Sterile
			80	10	Sterile
			110	380	Sterile
			140	80	Sterile
			170	70	Sterile
			200	Sterile	Sterile
			230	10	Sterile
			270	Sterile	Sterile
			300	Sterile	Sterile

*Necropsy*—The animals used in Part II were permitted to recover after every experiment, however, they died in from four to ten hours after the injection. In all cases the peritoneal cavity contained from 100 to 200 cc. of bloody fluid with flakes of fibrin. Both visceral and parietal peritoneum were intensely hyperemic and hemorrhagic.

#### COMMENT

Since it has been demonstrated that the intraperitoneal injection of gum tragacanth alone causes no ill effects, and that the intraperitoneal injection of *B. coli* in normal saline is followed by severe bacteremia but does not cause death, the question arises as to what is responsible for the death of the animals when *B. coli* suspended in gum tragacanth is injected intraperitoneally. To explain this we have formulated the hypothesis that the intraperitoneal retention of bacteria suspended in gum tragacanth favors the production of toxic substances, the absorption of which causes the death of the animal. When bacteria suspended

in saline are injected intraperitoneally, the production of toxin in an appreciable quantity is prevented by the rapid passage of the bacteria into the blood stream, where they are destroyed

The part played by the bacterial toxic substances as well as the influence of cellular reactions in this phenomenon are being investigated

#### SUMMARY AND CONCLUSIONS

1 Both blood and lymph of normal dogs were bacteria-free whether the animals had been fed or had fasted

2 Following the intraperitoneal injection of *B coli* suspended in physiologic sodium chloride, a large number of these organisms were found in the lymph (thoracic duct) and a relatively smaller number in the blood

3 Dogs, with thoracic duct intact, after receiving intraperitoneal injections with saline suspensions of *B coli*, rapidly developed a severe bacteremia but practically always survived

4 Following the intraperitoneal injection of *B coli* suspended in gum tragacanth, a small number of the organisms appeared in the lymph (thoracic duct), but none was detected in the blood

5 When dogs with the thoracic duct intact received intraperitoneal injections of *B coli* suspended in gum tragacanth, they did not have bacteremia, yet these animals invariably died

6 Bacteremia is not responsible for the death of dogs in acute *B coli* peritonitis

7 Rapid passage of bacteria from the peritoneal cavity into the blood was associated with the recovery of the animal

# SPLEENS FROM GAUCHER'S DISEASE AND LIPOID-HISTIOCYTOSIS

## THE CHEMICAL ANALYSIS <sup>1</sup>

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AND

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The clinical and anatomic differences between Gaucher's disease and lipoid-histiocytosis (type Niemann) have been pointed out by Mandelbaum and Downey,<sup>1</sup> Pick,<sup>2</sup> and one of us.<sup>3</sup> The purpose of this article is to report the striking differences that we have found in the chemical analyses of spleens from these two diseases

## MICROCHEMICAL ANALYSIS

In brief, the large cells in Gaucher's disease do not react positively to any of the usual staining reagents for lipoids. After mordanting in potassium bichromate, the large cells stain diffusely blue or yellowish orange with Nile blue or Sudan III. The intensity of the color is, however, of the same degree as the cells composing the remainder of the sections. In Niemann's disease, on the other hand, the large cells when fresh stain a rusty orange with Sudan III. In formaldehyde-fixed frozen sections of organs from Niemann's disease, the large cells stain a light, though definite, pale orange with Sudan III which becomes tinged with gray when the sections are counterstained with hemalum. When similarly prepared sections are treated with Weigert's iron-hematoxylin the large cells stain an intense black. If these sections are made into permanent mounts by passing them through absolute alcohol, the black cytoplasm appears distinctly vacuolated. Sections from Niemann's disease after mordanting in potassium bichromate show the large cells to be filled with various sized granules which stain a brilliant orange-

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<sup>1</sup> From the Snyder Fund and the Gusta Morris Rothschild Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research

1 Mandelbaum, F S, and Downey, H. The Cases of Gaucher's Disease Reported by Drs Knox, Wahl and Schmeisser, *Bull Johns Hopkins Hosp* **27** 109 (April) 1916

2 Pick, L. Ueber den Morbus Gaucher seine Klinik, pathologische Anatomie und histo-pathogenetische Umgrenzung, nebst Untersuchung ueber den Morbus Gaucher und ueber die Beteiligung des Skelettsystems, *Med Klin* **20** 1399, 1924, Zur Histiogenese der Gaucherzellen in der Milz, *Virchows Arch f path Anat* **254** 782, 1925, Der Morbus und die ihm aehnlichen Erkrankungen, *Ergebn d inn Med u Kinderh* **29** 519, 1926

3 Bloom, W. Splenomegaly (Type Gaucher) and Lipoid-Histiocytosis (Type Niemann) *Am J Path* **1** 595 (Nov) 1925

yellow with sudan III, and a deep purple-lavender with Nile blue sulphate. The Niemann cells stain positively with the method of Lorraine Smith-Dietrich. They do not react positively for soaps by the method of Fischler.

Gaucher cells may contain iron diffusely throughout the cytoplasm or in definite crystals, as demonstrated by the Turnbull blue method. The cells in Niemann's disease, however, do not give positive microchemical reactions for iron.

#### CHEMICAL ANALYSIS

The nature of the stored material in Gaucher's disease has been the subject of much controversy. Brill and Mandelbaum<sup>4</sup> and Mandelbaum and Downey<sup>5</sup> were the first to attempt actual chemical analysis of Gaucher material. Their results indicated that the stored material in Gaucher's disease was not cholesterol or one of the complex lipoids. Recently, Epstein<sup>6</sup> and Lieb<sup>7</sup> have obtained large amounts of a cerebroside from spleens of patients with Gaucher's disease. Lieb has isolated this cerebroside and found it to be kersasin. Cushing and Stout,<sup>8</sup> in a recent report of two cases of Gaucher's disease, have confirmed Lieb's observation on one of their cases. Wahl and Richardson<sup>9</sup> and Siegmund<sup>10</sup> have reported chemical analyses of splenic material from purported cases of Gaucher's disease. We believe that the cases they reported were instances, not of Gaucher's disease, but of that condition which we have called lipoid-histiocytosis (type Niemann). Siegmund found the spleen in his case to be rich in phosphatids.

#### MATERIAL AND METHODS

Our material consisted of a formaldehyde-fixed portion of spleen from a patient with Gaucher's disease, fresh and formaldehyde-fixed portions of a spleen from Niemann's disease, and a fresh portion of a slightly enlarged red spleen from a young adult with bronchopneumonia.

4 Brill, N. E., and Mandelbaum, F. S. Large Cell Splenomegaly (Gaucher's Disease). A Clinical and Pathological Study, *Am J M Sc* **146** 863 (Dec) 1913.

5 Mandelbaum, F. S., and Downey, H. The Histopathology and Biology of Gaucher's Disease (Large Cell Splenomegaly), *Folia hæmat* **20** 139 (March) 1916.

6 Epstein, E. Beitrag zur Chemie der Gaucherschen Krankheit, *Biochem Ztschr* **145** 398, 1924.

7 Lieb, H. Cerebroside-speicherung bei Splenomegalie, Typs Gaucher, *Ztschr f physiol Chem* **140** 305, 1924.

8 Cushing, E. H., and Stout, A. P. Gaucher's Disease, with Report of a Case Showing Bone Disintegration and Joint Involvement, *Arch Surg* **12** 539 (Feb) 1926.

9 Wahl, H. R., and Richardson, M. L. A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant, *Arch Int Med* **17** 238 (Feb) 1916.

10 Siegmund, H. Lipoidzellenhyperplasie der Milz und Splenomegalie Gaucher, *Verhandl d deutsch path Gesellsch* **18** 59, 1921.

The material from the latter was obtained at necropsy, while the other two spleens were removed at operation and fixed immediately. The fresh portion of the spleen from the patient with Niemann's disease and that of the so-called normal or control were ground by passing through a meat chopper shortly after removal from the body and then dried over a water bath. The material was further dried to constant weight in a vacuum desiccator. The same method of drying was applied to the fixed spleens. The dried powder from these spleens was then extracted for five days with ether in a Soxhlet. The residue was extracted with ethyl alcohol at 40 C for thirty-six hours. The material was further extracted at boiling temperature in a fresh portion of ethyl alcohol for five days. The ether soluble fraction was treated with acetone, the resulting precipitate of phosphatids filtered off, washed with acetone, and dried to constant weight in the vacuum desiccator. The acetone and ether were removed from the filtrate and the residue, containing cholesterol and fatty acids, dried to constant weight. The

TABLE 1—*Total Nitrogen, Phosphorus and Extractives*

	Moisture	Nitrogen, Gm per 100 Gm of Dry Spleen	Phos- phorus, Gm per 100 Gm of Dry Spleen	Ether Soluble, Gm per 100 Gm of Dry Spleen	Alcohol Soluble, Gm per 100 Gm of Dry Spleen	Total Extractives, Gm per 100 Gm of Dry Spleen
Niemann, fresh	76.7	8.968	3.974	32.316	36.525	63.841
Niemann, fixed	83.7	8.809	3.932	25.663	24.742*	50.405
Gaucher, fixed	84.5	11.332	1.683	7.501	22.400	29.901
Control, fresh	81.4	12.925	1.287	5.285	17.566	22.851

\* Some of this material was lost

two alcohol fractions were worked up separately, the alcohol being removed and the residue dried to constant weight. In the analysis of the materials obtained, nitrogen was determined by the Kjeldahl-Gunning method, fatty acids by the gravimetric method, the iodine number by the Hanus micromethod, phosphorus by the method of Briggs,<sup>11</sup> and cholesterol<sup>12</sup> by the method of Bloor, Pelkan and Allen.<sup>13</sup> The determinations were made in duplicate, the figures given in the tables being averages.

## RESULTS

The results of the various determinations are summarized in the accompanying tables. These show that there was a marked difference in the lipid extractives in the several spleens. In Niemann's disease

11 Briggs, A. P. Some Applications of the Colorimetric Phosphate Method, *J Biol Chem* **59** 255 (March) 1924.

12 Cholesterol was determined by two methods, the colorimetric method given above, and also by weighing the nonsaponifiable portion of the ether alcohol extract. The results of the two methods agreed closely.

13 Bloor, W. R., Pelkan, K. F., and Allen, D. M. Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J Biol Chem* **52** 191 (May) 1922.

the combined ether and alcohol soluble fractions in the fresh spleen totaled about 70 per cent, while in the fixed spleen they amounted to 50 per cent plus. This lower figure is in part due to the fact that some of the material was lost, as is indicated in table 3. In Gaucher's disease the total lipoids amounted to 30 per cent, and in the normal fresh spleen they were 23 per cent of the dry spleen. The nitrogens of the dry spleen of the Gaucher patient and of the normal person were about equal, with approximately 12 per cent, whereas the nitrogen of the Niemann fresh and fixed spleens was a little less than 9 per cent. As can be seen from table 1, the Niemann spleen, however, contained about three times as much phosphorus as the Gaucher or the normal.

TABLE 2—*Ether Soluble Fraction*

	Acetone Precipitate			Acetone Filtrate		
	Grams per 100 Gm of Dry Spleen	Nitrogen, Phosphorus, Gm per 100 Gm of Dry Spleen	Gm per 100 Gm of Dry Spleen	Choles- terol	Fatty Acid	Iodine Number
Niemann, fresh	18.210	1.108	0.502	8.308	3.462	62.4
Niemann, fixed	12.983	0.659	0.473	7.771	2.367	55.4
Gaucher, fixed	3.448	0.180	0.051	2.573	1.286	76.9
Control, fresh	3.324	0.288	0.099	2.424	1.039	124.2

The acetone filtrate of the ether fraction showed that the Niemann's disease material contains three and one-half times as much cholesterol as the Gaucher and normal spleens. The cholesterol values in the latter two were almost identical. The acetone precipitate of the ether soluble fraction, which can probably be figured as lecithin, showed approximately five times as much in the Niemann disease specimen as in the other two. The question arises as to how much of the alcohol soluble portion is to be counted as phosphatid.

On the Gaucher spleen we repeated Lieb's method for the extraction of kerafin and have verified his conclusions. We obtained for this fraction 7.447 Gm per hundred grams of dried spleen. Four-tenths gram of the precipitate from the 40° C alcohol fraction was dissolved in 100 cc of alcohol. To this were added 30 cc of cold saturated mercuric chloride. This gave a colorless gelatinous precipitate, much like egg-white in appearance, which filled the entire solution. The precipitate removed by filtration was suspended in methyl alcohol and hydrogen sulphide was passed through the suspension. The precipitate was filtered off, the filtrate boiled with charcoal and filtered again. The filtrate when concentrated and cooled gave an almost white, gelatinous precipitate. Under the microscope this appeared as round crystals arranged radially about a nucleus. This material had a somewhat indefinite melting point which seemed sharpest at 178° C. On hydrolysis of the material for eight hours in methyl alcohol and sulphuric acid

under a reflux condenser, we obtained a white, crystalline material with a melting point of 56.7 C. This corresponds very closely to that of the methyl ester of lignoceric acid. We found the melting point of the acid when separated from the methyl ester by saponification in methyl alcohol to be at 76 C. This is somewhat low for lignoceric acid, but we had insufficient material to purify it further.

Certainly in the case of the Gaucher material a part of the alcohol soluble fraction is precipitable with mercuric chloride as kerasin. In Niemann's disease, however, the amount of this fraction precipitated by mercuric chloride is so small that it cannot be handled. This fact, together with the high phosphorus value of this fraction, leads us to the conclusion that in Niemann's disease by far the greatest portion of the alcohol soluble fraction must be phosphatid.

TABLE 3—*Alcohol Soluble Fraction*

	Alcohol Soluble					
	Alcohol Soluble, Gm per 100 Gm of Dry Spleen		40 C Fraction		Boiling Fraction	
			Nitro gen, Gm per 100 Gm of Dry Spleen	Phos phorus, Gm per 100 Gm of Dry Spleen	Nitro gen, Gm per 100 Gm of Dry Spleen	Phos phorus, Gm per 100 Gm of Dry Spleen
	40 C Fraction	Boiling Fraction				
Niemann, fresh	25.783	10.742	1.779	0.589	1.150	0.829
Niemann, fixed	17.236*	7.506		0.523		
Gaucher, fixed	12.512	9.888		0.073†, 0.177		0.037
Control, fresh	6.677	10.889		0.107	1.150	0.063

\* Some of this material was lost.

† The first lot gave the low value, which is comparable to that found in the literature for lignoceric acid, but a second lot gave a much higher figure.

From the foregoing analyses it appears that the stored material in Gaucher's disease is constituted for the most part by kerasin, as was first shown by Lieb. In Niemann's disease, in view of the high phosphorus values of the ether and alcohol fractions, we may conclude that the stored material in this condition consists of lecithin and other phosphatids, to the extent of about 55 per cent of the dried spleen. There is an increase also in the quantity of unsaturated fatty acids present in Niemann's disease. The iodine number indicates that the spleen in this condition contains more unsaturated fatty acid than either the Gaucher or the normal spleen, the iodine number of the latter being double that of the Niemann material. The iodine number in Gaucher's disease is higher than in Niemann's disease, but considerably lower than in the control material.

The results of these analyses agree quite well with the microchemical study of the respective spleens, in which it was shown that none of the lipid reactions is given with any degree of typicalness in Gaucher's disease, while in Niemann's disease the staining reactions are highly indicative of the phosphatid group.

## SUMMARY

A few cases of a form of large cell splenomegaly, for which the name lipoid-histiocytosis is proposed, have in the past been erroneously reported as examples of Gaucher's disease. The anatomic differences between the two conditions have been previously published.

The microchemical reactions of the material present in the large cells in lipoid-histiocytosis (Niemann's disease) indicate that this material is lipoid in character and probably belongs to the phosphatid group.

In Gaucher's disease the large cells do not give any of the lipoid reactions in typical manner. They usually give the reaction for iron.

Chemical analyses prove the spleen of Niemann's disease to contain less total nitrogen than the Gaucher or the normal spleen, but a decidedly increased amount of phosphorus. The total ether and alcohol soluble extractives are also greatly increased in Niemann's disease.

The stored material in lipoid-histiocytosis is chiefly phosphatids, probably lecithin, and cholesterol. In Gaucher's disease the material is chiefly kersin.

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## CORRECTION

In the paper by Drs. Koessler and Lewis, "Determination of Bonchospasm in the Guinea-Pig" (*ARCH. INT. MED.* 39:163 [Feb.] 1927), the word "atrophine" in the legends for Figs. 3, 6 and 8 should read "atropine."

In the article by Drs. Koessler, Lewis and Walker, "Pharmacodynamic Actions of Bacterial Poisons," in the same issue, on page 198 the third line at the top should be struck out, and the following should be inserted as the second line in the second paragraph: "purulent exudates studied. Of thirty-seven specimens examined, only" also, the word "trymine," in the second line on page 213, should be "tyramine."

## Book Reviews

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THE ART AND PRACTICE OF MEDICAL WRITING By GEORGE H. SIMMONS, M.D., Editor and General Manager Emeritus, American Medical Association, and MORRIS FISHBEIN, M.D., Editor, The Journal of the American Medical Association Price, \$1.50 Pp 163 Chicago A. M. A. Press, 1926

Confession is free and general that medical writing in the United States of America is inferior to that of other cultured countries, and the relation of this inferiority to faults in our method of education is equally freely recognized. While waiting and hoping for an improvement in fundamentals, those now writing or about to write on medical subjects may be assured that a careful study of this little work can prevent many errors and add much to the force and the finish of their literary productions. Even those who do not write, but who read medical periodicals can improve their critical sense and enlarge their point of view by reading here why certain styles or methods in current medical literature are good and others bad. The qualifications of the authors do not require lengthy explanation. Dr. Simmons was for many years editor of the best edited medical weekly in any language, a journal that went through many of the disorders of literary infancy as to spelling and style before it reached its present plane. Dr. Fishbein is well known as a worthy successor in the editorial chair, and a brilliant original medical essayist. The first chapter on "An Acceptable Paper," sets forth with great accuracy and considerable humor the leading principles in medical composition. In the next one on "Style," the hackneyed extracts familiar in the compends on the subject are boldly omitted, but the trenchant advice given should be of great help to the beginner or to the veteran, if he is not too hardened in error.

In "The Subject and the Material," all the varieties of medical writing are explained clearly. In later chapters, there is valuable advice concerning titles, on the misuse of "case," "temperature," "pathology" and many other words, on spelling, hyphens, adjective endings, capitalization, abbreviations, numbers and figures. The chapter on "Prescriptions" is brief, that on "Securing a Bibliography" admirable, and should be put in the hands of all medical undergraduates, while those on "Preparation of the Manuscript," "Illustrations," "Charts and Tables" could be reread often with benefit by most writers. Equally practical are chapters on "Revision and Proofreading." Supplements giving the list of periodicals included in the "Cumulative Index" and "Bibliographic Abbreviations" should be referred to by all who write or correct papers containing such titles. The work is an admirable memorial to the editor emeritus and his lifework.

MODERN VIEWS ON DIGESTION AND GASTRIC DISEASE, MODERN MEDICAL MONOGRAPHS By HUGH MACLEAN, M.D., D.Sc., M.R.C.P., Professor of Medicine, University of London Cloth Price, \$4 Pp 170, with 14 charts and 23 figures New York Paul B. Hoeber, 1925

This is but one of several small volumes on the physiology of digestion and the treatment of gastric disease which have appeared in the press during the past year or more. Perhaps this is accounted for because of the widespread prevalence of both functional and gastric disease, the great increase in knowledge of gastric function and mechanics as a result of experimental investigation and the recognition of the importance of the correlation of clinical observations with advances in physiologic knowledge.

The book is written for the general practitioner, it is too short, concise and elementary for the student of today. Only the usual diseases are considered. Concerning that often discussed topic, "the medical versus surgical treatment of ulcer," the author states, "Surgery should never be resorted to in ulcer cases until medical treatment has failed." Sometimes obvious physical changes may be present that could not possibly be influenced by any method except a surgical one. In such cases, the sooner an operation is performed, the better. On the other hand, I should like to emphasize the fact that no case of ulcer should be operated on until a thorough trial has been given to medical treatment. It is really surprising how excellent the result of such treatment is in many of these cases, even when *apparent* pyloric obstruction is present. Such obstruction may arise from inflammatory exudation, and, on treating the ulcer, this obstruction may disappear spontaneously." He stresses the importance of the use of alkalis in the treatment of the majority of organic and functional gastric diseases.

VAGOTONIES, SYMPATHICATONIES AND NEUROTONIES By A. C. GUILLAUME  
Price, 14 francs Paris: Masson et Cie, 1925

This book is the first to appear in French which gives a thorough and comprehensive explanation of the terms in the title, being an etiologic, clinical and therapeutic study of the various disturbances in the equilibrium of the nervous system, especially in the sympathetic and the vegetative nervous systems.

Beginning with the vagotonia of Eppinger and Hess, Guillaume points out that this condition corresponds to the general condition classified as neuroses, and that the term must be limited and modified to describe the actual vagus disturbance as seen clinically, he shows, further, the relationship and contrast between true vagotonia and sympathicotonia.

There follows a precise and minute description of the conditions clinically, of the methods of examination and the morbid states following these disturbances, indicating the principal causes, such as infection, intoxication and pathologic conditions of the endocrine glands. He also indicates the therapy directed not only to the cause, but also toward the effects in the nervous system.

For the general practitioner the work is somewhat profound and specialized, but a careful and repeated study would help him to classify and treat many of the vasomotor and visceral symptoms, as well as psychic disturbances resulting from them, that are so often misunderstood and diagnosed as neuroses. It should be of decided interest and value for the specialist.

HYDROGEN ION CONCENTRATION By L. MICHAELIS. Authorized translation of the second revised and enlarged German edition by W. A. PERLZWEIG.  
Pp. 299. Price, \$5. Baltimore: Williams & Wilkins Company, 1926.

For a number of years this monograph written in German by Michaelis has been a standard reference for workers in physical chemistry. The translation of the second edition should have a wide circulation among American students in this field. The ten chapters revised by Michaelis to include the most significant recent advances are arranged in two parts. The first five chapters constitute part one and deal with the chemical equilibrium of the ions as follows: the laws of electrolytic dissociation, the theory of the quantitative determination of acidity and alkalinity, the dissociation of strong electrolytes, the state of dissociation of acids and bases during actual salt formation and electrolytic dissociation in nonaqueous solutions. Part two is a discussion of the ions, particularly the H-ions, as sources of electric potential differences, and the titles of these chapters are the electrode potentials, diffusion potentials, potentials at phase boundaries, membrane potentials, and adsorption potentials and electrokinetic phenomena. As stated, this book is primarily intended for students and workers in physical chemistry, and for these, it is invaluable.

DIATHERMY WITH SPECIAL REFERENCE TO PNEUMONIA By HARRY EATON STEWART, M.D., Attending Specialist in Physiotherapy, U S Marine Hospital, New York Second edition, revised and enlarged Price, \$3 Pp 228 New York Paul B Hoeber

This second edition, as indicated by the title, is especially devoted to a discussion of the value of diathermy in pneumonia The author's reports are most interesting and apparently fairly well controlled

Pneumonia has been a fertile field for investigators interested in therapeutics Various "cures" have appeared at frequent intervals In reading these reports it was difficult or impossible to detect error in the control technic, yet time has shown that there was some error as others failed to confirm the results

Past failures, however, while creating skepticism should not lead to the rejection of new methods Stewart's report should stimulate others who have adequate facilities for securing controls to try diathermy Time will tell whether his results can be verified

TISSUE CULTURE By ALBERT FISCHER Pp 315, with 70 illustrations and 1 colored plate Price, \$7.50 Copenhagen Levin & Munksgaard, 1925

This monograph is a summary of the work on tissue cultures The introductory chapters consider briefly the development of these studies Then follows an account of the culture medium and the preparation of cultures for microscopic examination Other chapters give methods for obtaining pure cultures of tissues, the use of tissue cultures for observing the effects of the body fluids, the interaction of various tissue cells in vitro and in morphogenetics. The final chapter considers tissue culture as a means for studying pathologic changes, immunity, the interaction of bacteria and tissues, cytotoxins and finally tumors

A GUIDE FOR DIABETICS By W R CAMPBELL and M T PORTER, Toronto Cloth Price, \$2.50 Pp 131 Baltimore Williams & Wilkins Company

The details which are desirable for a person with diabetes to learn cause physicians either to follow the principles and manual of one of the leaders in this field or to reduce their own views to mimeographed or printed form Here are 131 blank pages on which the patient can make notes, alternating with 131 pages of text Four-fifths of this text deals with food, only one-fifth with medical aspects These are stated soundly As between this and previous guides by other reputable men, the choice is largely a choice of the man one wishes to follow

## HYPERTENSION IN PREGNANCY

### RELATION OF THE CALCIUM CONTENT OF THE BLOOD TO THE ETIOLOGY \*

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A thorough analysis of the theories of the etiology of hypertension will not be undertaken in this article. In all probability the etiology of vascular disease varies in different cases and is the result of a combination of insults to the circulatory apparatus.<sup>1</sup> With the field limited to the hypertensions occurring in pregnancy, still another set of theories has been evolved,<sup>2</sup> the gist of which is the view that hypertension in pregnancy is a manifestation of the reaction to an intoxication. The exact nature and source of the toxemia is still unknown.<sup>3</sup>

Lange<sup>4</sup> and others,<sup>5</sup> and more recently Strouse and Daly<sup>6</sup> have emphasized the importance of thyroid intoxications in pregnancy. That the parathyroid glands should be similarly upset is not unlikely. It is well known that in parathyrioprivia an increased muscular tone is evident.<sup>7</sup> Associated with this phenomenon is a lowered concentration of calcium in the blood, first pointed out by Salvesen,<sup>8</sup> and since confirmed by numerous investigators.<sup>9</sup> Collip and his co-workers<sup>10</sup> have

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\* From the medical clinic of the Chicago Lying-In Hospital and Dispensary, aided by a grant from the Mothers' Aid Society.

1 Post, W E, and Stieglitz, E J. *Am J M Sc* **171** 648 (May) 1926.

2 DeLee, J B. *Principles and Practice of Obstetrics*, Philadelphia, W B Saunders Company, 1918.

3 Kane, H F. *Surg Gynec Obst* **42** 569 (April) 1926.

4 Lange, quoted by DeLee (footnote 2).

5 Ward, G G. *Surg Gynec Obst* **9** 617, 1909.

6 Strouse, S, and Daly, P. *Thyroid During Pregnancy*, *J A M A* **84** 1798 (June 13) 1925.

7 Fisher, N F, and Larson, E. *Am J Physiol* **75** 93 (Dec) 1925. Hoag, L A, and Rivkin, H. *Treatment of Infantile Tetany with Parathyroid Extract*, *J A M A* **86** 1343 (May 1) 1926. Berman, L. *Am J Physiol* **75** 358 (Jan) 1926.

8 Salvesen, H A. *J Biol Chem* **56** 33, 1923.

9 Greenwald, I, and Gross, J. *J Biol Chem* **64** 161, 1925. Moritz, A R. *J Biol Chem* **64** 81 (May) 1925. Berman, L. *Am J M Sc* **171** 245 (Feb) 1926. Greenwald I. *J Biol Chem* **67** 1 (Jan) 1926.

10 Collip, J B. *J Biol Chem* **63** 395 (March) 1925. Collip, J B, and Clark, E P. *J Biol Chem* **63** 461 (March) 1925. Collip, J B, Clark, E P, and Scott, J W. *J Biol Chem* **63** 439 (March) 1925. Berman, L. *J Lab & Clin Med* **11** 412 (Feb) 1926.

demonstrated an active parathyroid hormone capable of elevating the blood calcium content<sup>11</sup> This hormone is so potent that its use should be attended with great caution, as an excess may give rise to a dangerous hypercalcemia<sup>12</sup> Engelbach<sup>13</sup> believed in a physiologic relationship between hypocalcemia, parathyroid deficiency and hypertension Kylin<sup>14</sup> and his co-workers<sup>15</sup> and Reid<sup>16</sup> have presented evidence that there is a distinct relationship between a hypocalcemia and an elevation of the blood pressure Kylin also observed a hypercalcemia in diabetes with hypotension<sup>17</sup> Schmitz, Rohdenburg and Myers<sup>18</sup> and Anderson<sup>19</sup> demonstrated a low calcium concentration in chronic nephritis with hypertension

Furthermore, during pregnancy there is an active calcium anabolism in the fetus with a corresponding drain on the maternal blood and tissue calcium<sup>20</sup> Previous reports on the status of calcium of the blood in pregnancy have been somewhat conflicting Handelsman, Rose and Sherwin<sup>21</sup> found the concentration normal but lowered after parturition That this fall is not due to the hemorrhage attendant on the delivery is shown by the results of Swingle and Werner,<sup>22</sup> who showed that bleeding caused a rise in the blood calcium with a transient disappearance of tetany in parathyroidectomized dogs Feinberg and Lash<sup>23</sup> in a short series of eclamptic and control cases could demonstrate no relationship between the blood calcium content and the convulsions

11 Sherill, J W, and Copp, E F F *California & West Med* **24** 133 (Feb) 1926

12 Hjort, A M, Robinson, S C, and Tendick, F H *J Biol Chem* **65** 117 (Aug) 1925 Snell, A M Parathyroid Extract in Treatment of a Case of Tetany, *J A M A* **85** 1632 (Nov 21) 1925 The Parathyroid Hormone—A Warning, editorial, *J A M A* **86** 351 (Jan 30) 1926

13 Engelbach, W Arterial Hypertension Associated with Endocrine Dyscrasia, *J A M A* **74** 1619 (June 12) 1920

14 Kylin, E *Klin Wchnschr* **4** 806 (April 23) 1925

15 Kylin, E, and Myhrman, G *Klin Wchnschr* **4** 1870 (Sept 24) 1925 Kylin, E, and Myhrman, G *Deutsches Arch f klin Med* **149** 354, 1925

16 Reid, W D *Boston M & S J* **192** 883 (May 7) 1925

17 Kylin, E *Zentralbl f inn Med* **47** 79 (Jan 23) 1926

18 Schmitz, H W, Rohdenburg, E L, and Myers, V C Inorganic Phosphorus and Calcium of Blood in Nephritis, *Arch Int Med* **37** 233 (Feb) 1926

19 Anderson, W T *Hospitalstid* **68** 1177, 1925

20 The Need of Calcium, editorial, *J A M A* **85** 1065 (Oct 3) 1925

21 Handelsman, I, Rose, A, and Sherwin, C P Blood Changes in Antepartum and Postpartum Period of Young Mothers, *Arch Int Med* **37** 725 (May) 1926

22 Swingle, W W, and Werner, W F *Am J Physiol* **65** 372 (Jan) 1926

23 Feinberg, S M, and Lash, A F *Surg Gynec Obst* **42** 255 (Feb) 1926

Hypocalcemia has been demonstrated in other states of smooth muscle spasticity, such as pertussis,<sup>24</sup> asphyxia<sup>25</sup> and asthma<sup>26</sup>. There is some contradiction to this in pertussis<sup>27</sup>. Anderson and Graham<sup>28</sup> assert that tetany in babies is not parallel to a hypocalcemia but is associated with an alkalosis. A hypercalcemia is present in suppurating infections<sup>29</sup> and gout<sup>30</sup>. Late tuberculosis is associated with hypocalcemia<sup>31</sup> and is said to be benefited by therapy with calcium chloride.

Evidence has been presented which indicates that a metabolic disturbance associated with a hypocalcemia may be one etiologic factor in hypertension and in other conditions of increased smooth muscle tonus. If this is the case, the hypocalcemia should be most conspicuously manifest in the hypertensions of pregnancy, in which condition a maternal depletion of calcium takes place. That the parathyroid glands are intimately associated with calcium metabolism is clearly demonstrable. A relatively comprehensive objective study of the blood pressure and blood calcium determinations in a series of pregnant women was therefore undertaken to determine, if possible, any relationship between the two phenomena.

#### METHODS

The present investigation deals with the results obtained in 222 blood calcium determinations from a series of cases, including normal pregnant patients, pregnant patients with hypertension, and also some nonpregnant controls. The arterial tension was observed in each instance at the time the blood specimens were obtained. The analytic method was that developed by Tisdall,<sup>32</sup> modified by Clark and Collip<sup>33</sup> and later by Tweedie<sup>34</sup>. So far as possible the specimen and arterial tension readings were obtained at a uniform time of day, usually in the midafternoon.

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24 Powers, G. F. Tetany as a Cause of Convulsions in Whooping Cough, *Am J Dis Child* **30** 632 (Nov.) 1925.

25 Binet, L., and Blanchetiere, A. *Compt rend Soc de biol* **93** 511 (July 24) 1925.

26 Brown, G. T., and Hunter, O. B. *Ann Clin Med* **4** 299 (Oct.) 1925.

27 Regan, J. C., and Tolstouhov, A. Significance of Blood Chemical Changes in Pertussis, *J A M A* **86** 1116 (April 10) 1926.

28 Anderson, G. H., and Graham, S. G. *Quart J Med* **18** 62 (Oct.) 1924.

29 Schulze, F., and Scheller, E. *Arch f klin Chir* **136** 763, 1925.

30 Horowitz, P. *Am J M Sc* **171** 560 (April) 1926.

31 Teplitz, M. M. *Am Rev Tuberc* **7** 222 (Nov.) 1925. Schoenheit, E. W. *Am J M Sc* **170** 689 (Nov.) 1925. Pinkhof, J. *Nederl Tijdschr v Geneesk* **1** 230 (Jan 16) 1926. Piñerua, O. *Med Ibera* **20** 98, 1926.

32 Kramer, B., and Tisdall, F. F. *Bull Johns Hopkins Hosp* **32** 44 (Feb.) 1921. Kramer, B., Tisdall, F. F., and Howland, J. Calcium and Phosphorus in Serum in Relation to Rickets, *Am J Dis Child* **22** 560 (Dec.) 1921. Kramer, B., and Tisdall, F. F. *J Biol Chem* **47** 475 (Aug.) 1921. Tisdall, F. F. *J Biol Chem* **56** 439 (June) 1923.

33 Clark, E. P., and Collip, J. B. *J Biol Chem* **63** 461 (March) 1925.

34 Tweedie. To be published.

Hypertension cases in pregnancy may be grouped into four divisions,<sup>35</sup> as follows

1 A relatively benign type, occurring moderately early in pregnancy, characterized by a gradual rise in arterial tension and little evidence of serious intoxication. These are the so-called nephroses of pregnancy.

2 A late malignant type, occurring with a sudden unheralded onset, a rapid rise in arterial tension and evidences of marked intoxication, quickly becoming a true eclampsia, with hepatic as well as renal and vascular damage.

TABLE 1—*Relation of Average Blood Pressures at Varying Levels of Calcium Concentration*

Blood Calcium, Mg per 100 Cc	Average Blood Pressure		Number of Observations
	Systolic	Diastolic	
6-7	148	96	7
7-8	142	87	8
8-9	150	93	10
9-10	148	91	39
10-11	150	93	64
11-12	143	88	62
12-13	144	90	22
13-14	155	96	10
Total			222

TABLE 2—*Relation of Blood Calcium Concentration at Varying Blood Pressures*

Systolic Blood Pressure, Mm. Mercury	Average Blood Calcium	Number of Observations
90-100	12.1	2
100-110	10.7	10
110-120	10.7	24
120-130	11.1	25
130-140	10.5	23
140-150	10.3	34
150-160	10.1	37
160-170	10.6	24
170-180	10.1	15
180-190	10.9	13
190-200	11.1	3
200-210	11.2	7
210-220	12.4	1
220-230	11.8	2
230-240	9.8	2
Total		222

3 Hypertension in pregnancy in patients with preexisting vascular and usually renal disease, both undergoing exacerbation during the pregnancy.

4 Hypertension in pregnancy with definite complications, such as toxic goiter, cardiac disease, acute infections and the like.

The present series included twenty-nine cases of the first type, only one of the second or eclamptic group, sixteen of the third group, and one of the fourth. Four cases were classified as falling into both groups 1 and 3. Forty cases were studied as controls, including both the pregnant and the nonpregnant without hypertension.

## RESULTS

The comparison of the arterial tension levels to the calcium content of the blood may be carried out by two methods first, to determine the average arterial tension at given blood calcium concentrations and,

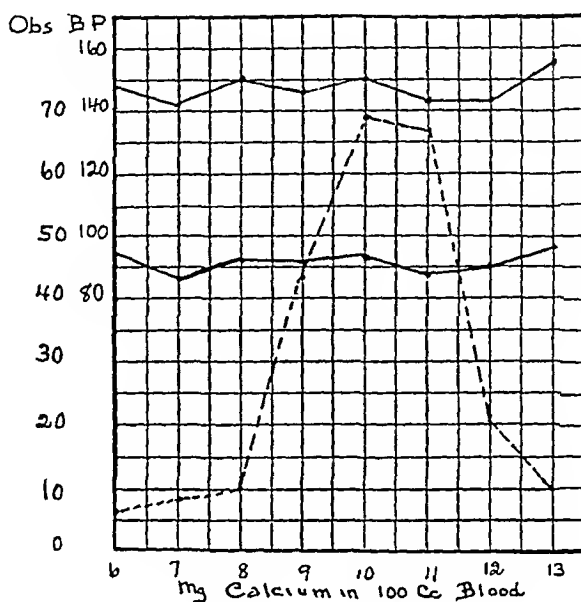


Chart 1—Average arterial tension at given blood calcium concentrations upper solid line, systolic, lower solid line, diastolic blood pressures, broken line, number of observations

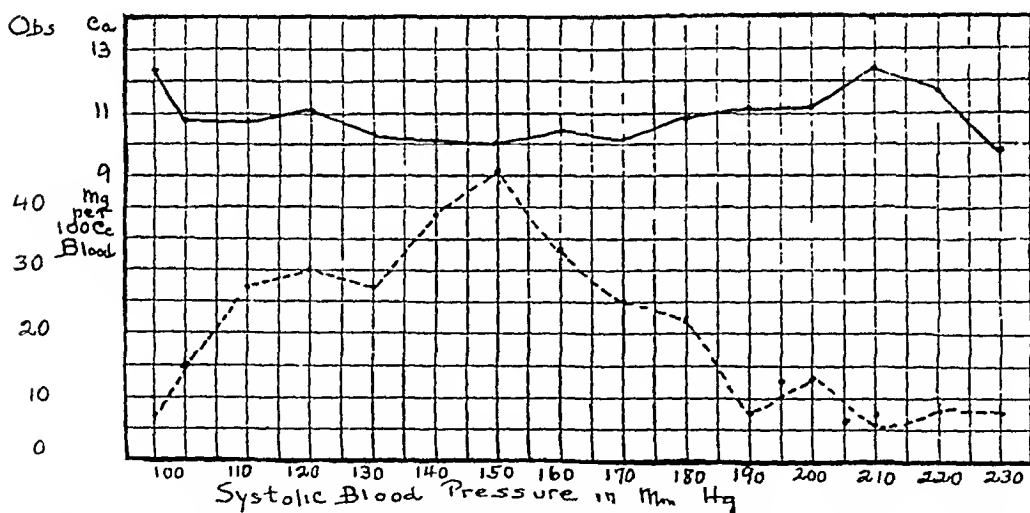


Chart 2—Average calcium content at different levels of vascular pressure solid line, blood calcium content, broken line, number of observations

second, to determine the average calcium content at different levels of vascular pressure. The results of such analyses appear in tables 1 and 2 and charts 1 and 2, incorporating all the determinations.

The tabulated and charted results reveal a definite lack of direct or indirect variation. The averages are remarkably uniform in either

method of comparison The averages of the blood calcium content coincide well with previously published results for normal persons<sup>36</sup> Eighty-eight per cent of the calcium determinations ranged from 9 to

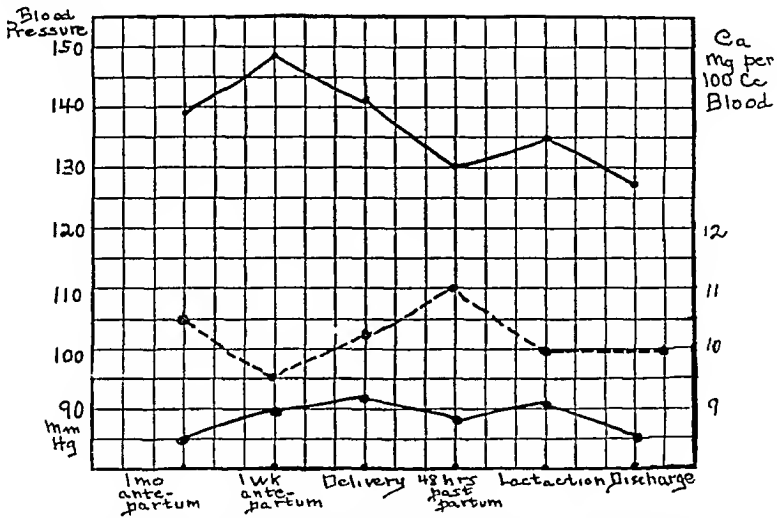


Chart 3—Curves of twenty-five cases from group 1 upper solid line, systolic, lower solid line, diastolic blood pressures, broken line, blood calcium content

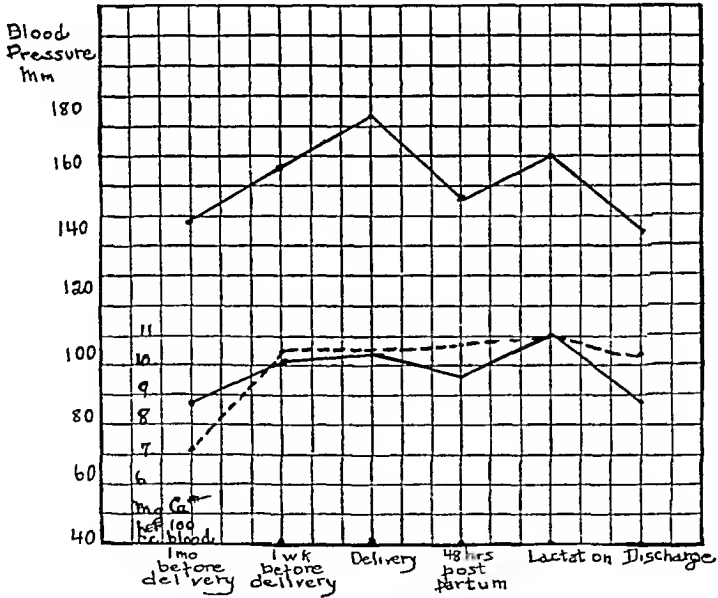


Chart 4—Curves from fourteen cases of preexisting vascular and renal disease upper solid line, systolic, lower solid line, diastolic blood pressures, broken line, calcium content

13 mg per hundred cubic centimeters of plasma, and 60 per cent fell between 10 and 12 mg Anderson<sup>19</sup> places the normal average at 107 mg per hundred cubic centimeters of plasma Pozzi<sup>37</sup> found no

36 Wyss, E Blood Calcium, Geneva letter, J A M A 86 1783 (June 5) 1926  
37 Pozzi, A Policlinico 32 503 (Oct) 1925

parallelism between the blood pressure and blood calcium in dogs after irradiation of the suprarenals. These results are essentially similar to those of Feinberg and Lash<sup>23</sup> in eclamptic cases.

However, averages of large series of figures are prone to obliterate fluctuations and therefore distort or conceal some true relationships. In

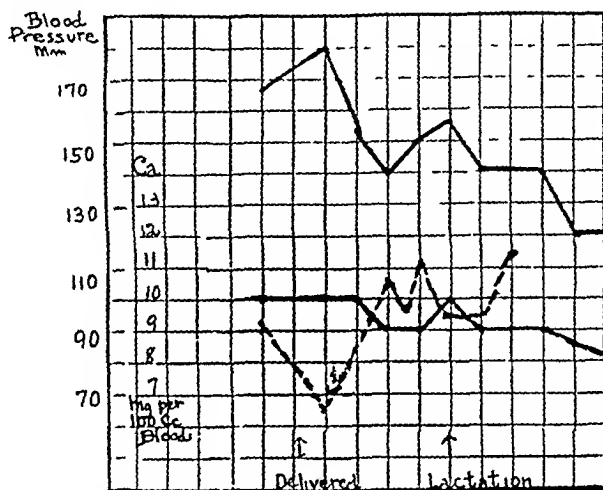


Chart 5—Record of patient HC 15—upper solid line, systolic, lower solid line, diastolic blood pressures, broken line, calcium content

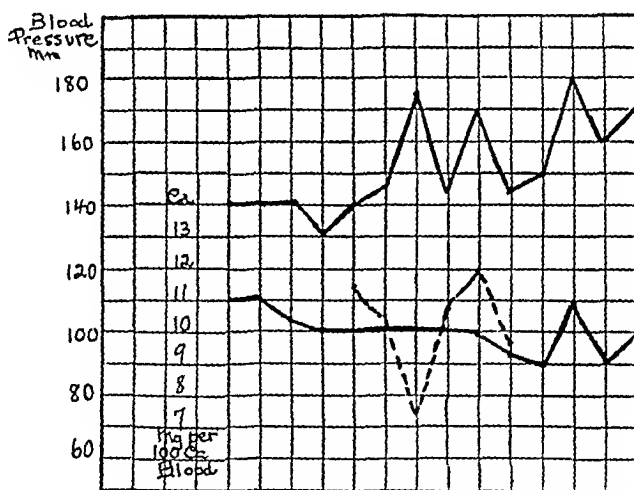


Chart 6—Record of patient HC 19 during pregnancy—upper solid line, systolic, lower solid line, diastolic blood pressures, broken line, calcium content

the course of these studies it was noted that a prompt postpartum fall in blood pressure occurred followed by a secondary rise with surprising regularity. The secondary rise occurred from fifty to one hundred hours after delivery and was coincident with the onset and establishment of lactation. In order to limit the study to one type of disturbance, data from twenty-five cases of the first group were tabulated. The results are given in chart 3.

These observations are of physiologic interest. They correspond to the results of Hetenyi,<sup>38</sup> who states that the blood calcium falls near the end of pregnancy. The analysis of the total averages demonstrated an absence of definite parallelism between a rising arterial tension and a diminishing calcium concentration in the blood. Therefore, in pregnancy at any rate, I am led to the conclusion that the latter factor is not a vital mechanism in the etiology of hypertension. However, in the third chart there is clearly an inverse relation between the arterial tension and the blood calcium. Particularly interesting is the rise in tension, with the corresponding moderate hypocalcemia which occurred so regularly coincident with the onset of lactation. That a physiologic relation exists is highly probable, especially in view of the fact that lactation brings about a sudden drain on the free circulating calcium, which is then more slowly compensated by a metabolic readjustment. In the group of fourteen cases with preexisting vascular and renal disease a similar curve was obtained, although there was no definite relationship to the calcium content of the blood (chart 4).

Another noticeable difference is the greater height of both the systolic and the diastolic averages. This is characteristic of the group, those patients with vascular disease existing before their pregnancy may, and usually do, have blood pressures so high that ignorance of the pre-existing disease may cause great alarm.

Two charts of individual cases (HC 15 and HC 19) reveal a similar parallelism between an elevation in arterial tension and a hypocalcemia. Other cases showed no such association.

The greatest degree of hypocalcemia occurred in a case of severe chronic glomerular nephritis with moderate hypertension, both conditions being aggravated markedly by the pregnancy.

#### COMMENT

These investigations demonstrate a lack of constant variation between the calcium concentration of the blood plasma and the arterial tension and reveal relatively normal calcium values irrespective of hypertension in pregnancy. Therefore, the conclusion that hypocalcemia is not a major etiologic factor in pathologic hypertension is warranted. However, a clear relationship exists between minor variations in arterial tension and the blood calcium content. This is strikingly demonstrated in chart 3. Such a relation has considerable physiologic significance and coincides with many previous observations of a relative hypocalcemia in clinical states associated with an increased tone of smooth muscle fibers. That the appearance of the secondary rise in arterial tension and fall in calcium content simultaneously with the onset of

lactation is more than purely coincidental is highly probable. The sudden drain on free blood and tissue calcium, with the resultant hypocalcemia, explains this phenomenon. The occurrence of physiologic variations in blood pressure is not necessarily due to the same mechanism as pathologic hypertension.

Therapeutically numerous attempts have been made to cause an increase in the blood calcium. Addison and Clark<sup>39</sup> report a fall in arterial tension, associated with diuresis and acidosis on the administration of calcium and potassium chlorides. Singer and others<sup>40</sup> similarly report a fall in the blood pressure, a slowing of the cardiac rate and diuresis following the therapeutic use of calcium lactate. However, it must be recalled that calcium slows the heart and that this in itself may be the explanation of the falling blood pressure. Hjordt<sup>41</sup> showed calcium salts to be absorbed on administration by mouth, but Orr, Holt, Wilkins and Boone<sup>42</sup> and Briggs<sup>43</sup> demonstrated that this caused a reduction of the amount of phosphate in the blood and urine, by the precipitation of calcium phosphate in the bowel. Briggs emphasized that this reduces the synthesis of ammonia by the kidney, thereby reducing the renal load. However, in the absence of evidence that hypocalcemia is the fundamental cause of the hypertension, therapy directed toward raising the level of the blood calcium is not strongly indicated. True, pregnancy is associated with a maternal depletion of calcium, which must be replaced. Dietary management, however, suffices for this.

The observations of Remond<sup>44</sup> that calcium concentration falls during active growth of cancer cells and rises during regression is of interest in connection with rapid fetal growth, with the gradually increasing moderate hypocalcemia near the termination of pregnancy and the rise again during uterine involution.

#### SUMMARY

Hypocalcemia is not of major etiologic significance in arterial hypertension in pregnancy, despite the fact that in such cases the relationship should be most conspicuous.

39 Addison, W. L. T., and Clark, H. G. *Canad. M. A. J.* **15**: 913 (Sept.) 1925.

40 Singer, G. *Wien. med. Wchnschr.* **34**: 247, 1921. Loewenstem, W. *Klin. Wchnschr.* **5**: 354 (Feb. 26) 1926.

41 Hjordt, A. M. *J. Biol. Chem.* **45**: 783 (Oct.) 1925.

42 Orr, W. J., Holt, L. E., Jr., Wilkins, L., and Boone, F. H. *Relation of Calcium and Phosphorus in Diet to Absorption of These Elements from Intestine*, *Am. J. Dis. Child.* **28**: 574 (Nov.) 1924.

43 Briggs, A. P. *Metabolic Aspects of Calcium Therapy*, *Arch. Int. Med.* **37**: 440 (March) 1926.

44 Remond, A. *Compt. rend. Soc. de biol.* **93**: 1061, 1925.

During the final month of pregnancy a gradual rise in arterial tension is associated with a moderate hypocalcemia

Immediately after parturition a fall in blood pressure occurs, with a corresponding rise in the blood calcium concentration

Coincident and probably associated with the onset of lactation a secondary elevation in arterial tension occurs, with a corresponding and equally transient hypocalcemia

The latter phenomenon permits of physiologic interpretation

# VITAL CAPACITY

## A STUDY OF THE EFFECT OF BREATHING DRY AIR \*

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CLEVELAND

It has been recognized that climates with a low relative humidity give relief to some patients with asthma. Inferentially this is due, at least in part, to the beneficial effect of dry air, which will extract more moisture from the bronchial tree than the air of a locality with a higher humidity. If this is true in respect to the bronchial moisture of asthma, it should also be true in respect to bronchial moisture from other sources, such as cardiac and renal.

The possible significance of this factor was seen in the course of experimentation on an entirely different problem. It happened that a patient with cardiac decompensation was asked to inspire through a jar of calcium chloride for a five minute period. The patient expressed his gratitude for the procedure because he felt so much better and could breathe more easily than before. The experimenters' curiosity being aroused, a number of patients with asthmatic, cardiac and renal diseases and a few with pulmonary infiltration were examined. A second series of one hundred patients, normal as to heart and lungs, served as a control.

The method consisted simply of taking the vital capacity on the Sanborn-Benedict metabolimeter before and after the patient breathed through a jar containing anhydrous calcium chloride. Three vital capacity readings were taken before and three after the breathing of dry air, and the highest of these was recorded in each instance. The chloride jar was connected to a face mask equipped with two-way valves so that only the inspired air passed through the jar. Expired air is presumably always saturated with moisture at body temperature. In breathing, dry air will extract more moisture from the bronchi than will room air, which already contains a certain amount of moisture. The amount of moisture in the expired air is not appreciably changed after dry air is discontinued, as shown by the following experiment. The amount of water collected in calcium chloride from the expired air before breathing dry air was 1.430 Gm per 25 liters, and after discontinuing dry air, 1.335 Gm. Carbon dioxide is not combined with calcium chloride, therefore it is a negligible factor.

The results obtained in the normal subjects are shown in table 1. There was an average increase of vital capacity of 12.5 cc, or 0.3 per cent after breathing dry air. Forty-four per cent of the patients

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\* From the Department of Medicine of Western Reserve University and Lakeside Hospital

responded with an increase of vital capacity. Of these, 45 per cent showed an increase from 110 to 308 cc, and 55 per cent, less than 100 cc. Fifteen per cent of the entire series showed no change after breathing dry air, and 41 per cent responded with a decrease of vital capacity. Of these, 14 per cent gave a decrease from 110 to 308 cc, and 86 per cent less than 100 cc. It will be noted that the greatest increase was 308 cc, or 84 per cent, and the greatest decrease likewise was 308 cc, or 76 per cent. Although 75 per cent of the patients showed no change after breathing dry air or varied to  $\pm$  100 cc, the change in the remaining 25 per cent requires explanation.

In this kind of an experiment, in which the personal factor is such an important element, it is hard to estimate when a patient has given his best cooperation. Some patients are overanxious to please while others are the reverse, and the results may be equally unreliable. Such factors may account for variations as great as 308 cc. On several occasions I became the subject, and an assistant found that my vital capacity remained exactly the same after breathing dry air. In these instances cooperation is not so questionable. There is another explanation which may be offered for those who gave a decrease of vital capacity after breathing dry air, namely, superventilation, which has been shown by Joannides<sup>1</sup> to decrease vital capacity. The patients were instructed to breathe normally, but in several instances respiration was deeper and more rapid than normal.

The criticisms mentioned above are applicable to the patients with bronchiolar edema, but in these cases there were criteria to prove the benefit of breathing dry air in addition to an increase of vital capacity. The least important of these criteria was the subjective improvement noted by a large proportion of the patients. In some cases this may have been influenced by suggestion, but in a number it was purely spontaneous. Most important, however, were the observations of physical signs before and after the experiment. If a patient experienced relief, almost invariably some change was noted in the number and character of the râles in the lungs, still more important, change was noted in the respiratory excursion of the chest and the lung volume.

The significance of the respiratory excursion of the chest has been pointed out by Hoover<sup>2</sup> and is particularly significant when properly applied in a study of these cases. He has shown that the movement of the costal margins during inspiration results from the combined effect of the intercostal muscles and the diaphragm. The effect of the intercostal muscles is to produce lateral movement of the rib ends and

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<sup>1</sup> Joannides, M. Effect of Dyspnea Variouslly Produced on Vital Capacity of Arch Int Med **33** 145 (Jan.) 1924.  
<sup>2</sup> Hoover, C. F. Diagnostic Lung Signs, Arch Int Med **20** 701 (Nov.) 1917.

TABLE 1—*Normal Cases*

Case	Vital Capacity Before Dry Air, Cc	Vital Capacity After Dry Air, Cc	Expected Vital Capacity, Cc	Gain or Loss in Cc	Gain or Loss in Percentage
1	4,750	4,730	4,400	— 20	—0.4
2	4,730	4,884	4,652	+154	+3.3
3	3,894	3,982	4,025	+ 88	+2.3
4	3,938	4,070	3,925	+132	+3.4
5	3,828	3,872	4,175	+ 44	+1.1
6	5,280	5,236	5,000	— 44	—0.8
7	4,576	4,444	4,375	—132	—2.9
8	4,752	4,730	4,350	— 22	—0.4
9	3,432	3,520	4,075	+ 88	+2.6
10	4,664	4,708	4,072	+ 44	+0.9
11	1,730	4,708	4,750	— 22	—0.4
12	3,696	3,652	3,850	— 44	—1.2
13	4,554	4,796	4,450	+242	+5.3
14	3,586	3,586	3,040	0	0.0
15	2,904	2,970	3,340	+ 66	+2.2
16	2,596	2,618		+ 22	+0.8
17	5,390	5,610	4,725	+220	+4.1
18	3,344	3,488	3,900	+144	+4.3
19	3,300	3,300		0	0.0
20	5,236	5,170		— 66	—1.2
21	3,872	3,850	4,225	— 22	—0.5
22	3,564	3,564	4,200	0	0.0
23	2,838	2,816	2,860	— 22	—0.7
24	4,466	4,466	4,550	0	0.0
25	3,476	3,432	3,975	— 44	—1.2
26	2,750	2,750	2,820	0	0.0
27	2,442	2,442	2,790	0	0.0
28	3,080	2,904	2,808	—176	—5.7
29	4,444	4,532	4,370	+ 88	+1.9
30	4,686	4,730	4,300	+ 44	+0.9
31	4,334	4,400	4,275	+ 66	+1.5
32	4,994	4,972	4,925	— 22	—0.4
33	3,036	3,168	3,560	+132	+4.3
34	3,300	3,300	3,552	0	0.0
35	2,640	2,530	2,660	—110	—4.1
36	2,596	2,596	2,587	0	0.0
37	4,180	4,180	4,125	0	0.0
38	4,114	4,202	4,400	+ 88	+2.0
39	5,192	5,148	4,850	— 44	—0.8
40	4,466	4,532	4,075	+ 66	+1.4
41	4,378	4,466	4,575	+ 88	+2.0
42	3,608	3,564	3,900	— 44	—1.2
43	3,652	3,608	4,027	— 44	—1.2
44	3,564	3,608	3,850	+ 44	+1.2
45	3,850	3,630	4,200	—220	—5.7
46	3,674	3,696	4,225	+ 22	+0.6
47	4,114	4,114	3,645	0	0.0
48	4,884	4,864	4,150	— 20	—0.4
49	2,640	2,728	2,880	+ 88	+3.3
50	3,542	3,520	3,500	— 22	—0.6
51	3,190	3,256	3,500	+ 66	+1.7
52	2,618	2,574	2,700	— 44	—1.6
53	5,148	5,082	4,325	— 66	—1.2
54	3,542	3,542	3,220	0	0.0
55	3,234	3,014	2,813	—220	—6.8
56	2,970	3,036	2,940	+ 66	+2.2
57	2,244	2,420	2,540	+176	+7.8
58	3,894	3,982	4,550	+ 88	+2.2
59	3,454	3,564	2,880	+110	+3.1
60	4,180	4,048	3,850	—132	—3.1
61	2,772	2,838	3,080	+ 66	+2.3
62	2,530	2,376	2,880	—154	—6.0
63	2,420	2,442	2,860	+ 22	+0.9
64	5,390	5,632	4,375	+242	+4.2
65	4,180	4,312	3,975	+132	+3.1
66	4,510	4,466	4,325	— 44	—0.9
67	3,652	3,960	4,275	+308	+8.4
68	5,325	5,475	4,500	+150	+2.8
69	3,718	3,718	4,625	0	0.0
70	2,618	2,662	3,160	+ 44	+1.5
71	4,004	3,696	5,250	—308	—7.6
72	3,820	3,520	4,675	—300	—7.7
73	2,046	2,222	2,520	+176	+8.6
74	3,674	3,630	3,000	— 44	—1.1
75	2,948	3,146	3,900	+198	+6.7
76	5,192	5,324	4,175	+132	+2.5
77	4,774	5,038	4,000	+264	+5.5
78	4,994	4,906	3,915	— 88	—1.8
79	2,838	2,860	3,575	+ 22	+0.7

TABLE 1—*Normal Cases—(Continued)*

Case	Vital Capacity Before Dry Air, Cc	Vital Capacity After Dry Air, Cc	Expected Vital Capacity, Cc	Gain or Loss in Cc	Gain or Loss in Percentage
80	4,488	4,334	4,150	-154	-3.4
81	2,904	2,904	3,475	0	0.0
82	5,390	5,148	4,100	-242	-4.4
83	3,454	3,432	3,500	-22	-0.6
84	3,498	3,256	3,800	-242	-6.9
85	3,542	3,564	3,180	+22	+0.6
86	5,016	5,126	4,500	+110	+2.1
87	2,926	2,882	3,200	-44	-1.5
88	3,168	3,168	2,760	0	0.0
89	3,498	3,300	2,980	-198	-5.6
90	3,938	3,872	4,300	-66	-1.6
91	4,312	4,488	4,250	+176	+4.0
92	5,588	5,566	4,300	-22	-0.4
93	3,256	3,234	3,892	-22	-0.5
94	3,630	3,848	3,850	+218	+3.5
95	4,400	4,400	4,400	0	0.0
96	3,476	3,410	3,300	-66	-1.2
97	3,696	3,542	3,320	-154	-4.1
98	3,674	3,696	3,397	+22	+0.5
99	4,620	4,554	4,275	-66	-1.0
100	5,082	5,390	4,250	+308	+6.6

that of the diaphragm, to produce medial movement. In a normal person the costal margin moves laterad because the balance of power is in favor of the intercostal muscles. This ascendancy of power is due to the mechanical disadvantage of the diaphragm which, because of its dome, exerts its traction in a curved rather than in a straight line between its points of origin in the central tendon and insertion at the costal margin. Anything which will depress the diaphragm, making the line of traction more nearly a straight line, will decrease the disadvantage and finally may give ascendancy of power to the diaphragm. Under such circumstances, the costal margin will move laterad to a lesser degree, become stationary or move mediad according to the degree of depression of the diaphragm. It should be kept in mind that enlargement of the heart or a pericardial effusion depresses only that part of the diaphragm attached to the costal margin from the ensiform process to the seventh costal cartilage, and pleural effusion or emphysema that part from the seventh costal cartilage laterally. Therefore, enlargement of the heart or pericardial sac limits the outward movement of the medial portion of the costal margin during inspiration, and an emphysematous lung or pleural effusion limits the movement of the lateral portion of the costal margin. A markedly emphysematous lung may affect also the entire costal margin. It is important to understand this conception of the effect of emphysema on the costal margins because otherwise a case like the following could not be explained. A patient with bronchiolar hypertonus and emphysema showed the entire extent of both costal margins moving mediad with inspiration, a tympanitic percussion note throughout the chest, low lung bases with no excursion during respiration, and a marked diminution of vital capacity. A dose of 1 cc of epinephrine hydro-

chloride subcutaneously gave an increase of vital capacity and good outward excursion of the costal margins during inspiration, but the lung bases remained at the same level and continued to show no excursion. This observation can be explained only on the basis of a marked emphysema of both lungs which depressed the diaphragm and resulted in mediad movement of the costal margins before the injection of epinephrine hydrochloride, and a marginal emphysema of the lung bases which persisted after the injection of the drug, but which was not sufficient to depress the diaphragm.

With this concept understood, the significance of changes in the movement of the costal margins after breathing dry air is obvious. If, as was found in many cases of emphysema, the costal margins were moving mediad before breathing dry air and laterad subsequently, only one conclusion could be reached, namely, that a diminution of lung volume had occurred as a result of the dry air. This diminution of emphysema could have been accomplished only by a lessening of bronchial moisture which had caused bronchial stenosis and thereby produced localized or generalized emphysema.

It is not conceivable that bronchial stenosis due to any other factor than moisture could be modified by dry air. Furthermore, it is equally inconceivable that vital capacity reduced by encroachment on, or limitation of, movement of the lungs could increase as a result of dry air. In myocardial failure with edema in the bronchial tree, however, there is abundant opportunity for some or all of the bronchi to become partially or completely stenosed, with a resultant emphysema. This is the type of case that will respond to dry air with an increase of vital capacity, a decrease of emphysema, an increased motility of the lung and chest wall and subjective improvement.

There are cases of mild cardiac decompensation which show a decreased vital capacity, but no moisture in the bronchi. Von Basch<sup>3</sup> in 1889 advanced the idea that increase of arterial pulmonary pressure caused a distention of the alveolar capillaries, thus producing a stiffening (Lungenstarheit) which interfered with expansion and retraction of the lungs. Siebeck<sup>4</sup> reached a similar conclusion. Recent work of Drinker, Peabody and Blumgart<sup>5</sup> gives credit to this theory, but it is considered less important in reducing vital capacity than the "inward swelling" (Lungenschwelling of von Basch) of the capillaries, which tends to diminish alveolar space. Lundsgaart<sup>6</sup> attributes the initial loss of vital capacity to increase of residual air, that is, stiffening of the lung.

<sup>3</sup> Von Basch, S. Wood's Medical and Surgical Monographs, vol 3, no 1, 1889.

<sup>4</sup> Siebeck R. Arch f klin Med **100** 204, 1910.

<sup>5</sup> Drinker, Peabody and Blumgart. J Exper Med **35** 77 (Jan) 1922.

<sup>6</sup> Lundsgaart, C. Determination and Interpretation of Changes in Lung Volumes in Certain Heart Lesions, J A M A **80** 163 (Jan 20) 1923.

In the later stages of decompensation, however, he attributes it entirely to diminished air space. If a lung is rigid because of engorged capillaries and interstitial edema, or the air space is limited by the "inward swelling" of the capillaries, no change could be expected from breathing dry air. If in addition to the factors mentioned above, there was also bronchial edema, there would be an increase of vital capacity caused by dry air in proportion to the amount of resultant bronchial stenosis.

A few selected cases will be illustrative of the above discussion.

#### REPORT OF CASES

CASE 2—L. C., aged 40, had a condition diagnosed as syphilitic aortitis, aortic insufficiency, aneurysm of the sinus of valsalva and myocardial insufficiency.

The costal margins were moving mediad before the experiment, and there were many râles in the lungs. The vital capacity was 2,134 cc before breathing dry air and 2,376 cc afterward, a gain of 242 cc, or 11.3 per cent. The expected vital capacity was 4,323 cc. The patient experienced considerable relief, and the costal margins were now moving laterad. There was no change in the number of râles.

In this case necropsy showed the aneurysm to be very small and the aorta not greatly dilated, therefore, neither could have produced bronchial stenosis. The only remaining factor for the production of stenosis and the resulting emphysema was moisture in the bronchial tree due to myocardial insufficiency. Breathing dry air decreased lung volume, as shown by the movement of the costal margins. An increase of vital capacity was additional proof of decreased emphysema. The vital capacity did not rise to normal because it was partly inhibited by lung rigidity caused by engorged capillaries and interstitial edema.

CASE 18—E. McT., aged 54, had a condition diagnosed as myocardial insufficiency, generalized arteriosclerosis, chronic myocarditis and chronic nephritis.

Examination showed crepitant and bronchial râles throughout the lower part of the chest. There was a slight amount of fluid in the left pleural cavity. The lateral portion of the left costal margin was stationary, but the medial portions and right lateral portion were moving laterad with inspiration. The expected vital capacity was 4,072 cc, but the actual only 1,452 cc. After the patient had breathed dry air for five minutes, the vital capacity was 1,496 cc. After a further nine minute period, it was 1,716 cc, a gain of 264 cc, or 18.2 per cent over the patient's vital capacity before breathing dry air. Breathing dry air was continued for six minutes more with a resultant vital capacity of 1,804 cc, a further gain of 88 cc, or 5.1 per cent. Thus there was a total gain of 352 cc, or 24.2 per cent. Examination at this time showed fewer of both types of râles, particularly the bronchial. The left lateral costal margin was now moving laterad freely with inspiration. The patient felt better and could breathe easier because he said, "There is less tightness in my chest."

On a later date, examination showed no râles in the lungs, good lateral excursion of the costal margins with inspiration and no respiratory difficulty. The vital capacity was now 3,630 cc, and dry air gave no increase.

In this case, nephritis could have been the cause of a reduced vital capacity, but it was the opinion that myocardial insufficiency was the most important factor in the production of bronchiolar moisture. There was no condition other than moisture to produce bronchiolar stenosis. The lateral portion of the left costal margin could have been limited in its outward excursion during inspiration by fluid in the pleural cavity on that side, but was due rather to localized emphysema of the left lower lobe, which was caused to disappear by breathing dry air. Here again, an increased vital capacity was a proof of the foregoing observations. The later experiment, when no increase of vital capacity was obtained, was performed at a time when emphysema was not present.

CASE 25—M S, aged 43, had a condition diagnosed as myomalacia cordis, coronary thrombosis and myocardial insufficiency

On the day of the experiment there was an undeterminable amount of fluid in both pleural cavities with emphysema of both upper lobes of the lungs and a few crepitant and bronchial râles. Both costal margins were moving medially in their entire extent. The expected vital capacity was 4,825 cc, and the actual only 1,474 cc. After breathing dry air, it rose to 1,672 cc, a gain of 198 cc or 13.4 per cent. The lateral portion of the right costal margin was now moving laterally. There was no change in the râles.

In this case there was nothing to account for bronchial moisture and stenosis except myocardial insufficiency. The diaphragm was depressed on both sides causing a medial movement of the costal margins. After breathing dry air, emphysema of the right lower lobe was decreased, and the costal margin on that side moved laterally with inspiration. Thus there was a combination of fluid and emphysema on the right side and fluid alone in the lower part of the left side of the chest. Dry air could not modify the decreased vital capacity due to the pleural effusion, but had an appreciable effect by decreasing the emphysema present in the right lower lobe.

CASE 38—T T, aged 49, had a condition diagnosed as auricular fibrillation with myocardial insufficiency, asthma and chronic emphysema.

The vital capacity before and after breathing dry air was 2,420 cc, and 2,706 cc, a gain of 286 cc, or 11.4 per cent. Before the experiment the costal margins were moving medially throughout their entire extent, and there were many bronchial râles. After the patient had breathed dry air, there were fewer râles, and both costal margins were moving strongly laterally with inspiration.

In this case a decrease of vital capacity could have been due to myocardial insufficiency, bronchiolar hypertonus or atrophic emphysema. Since the volume of the lung was changed markedly by breathing dry air as shown by costal margin movement, a part of the emphysema must have been due to partial stenosis of the bronchi by moisture.

CASE 42—C B, aged 54, had a condition diagnosed as exophthalmic goiter, chronic myocarditis with myocardial insufficiency, auricular fibrillation and arteriosclerosis with hypertension and emphysema.

On the day of the experiment the lung bases were at the level of the twelfth rib in the midscapular lines. The medial portions of the costal margins were moving medially and the lateral portions slightly laterally with inspiration. There were crepitant râles at the lung bases posteriorly. The vital capacity was 3,278 cc, and was not changed by quiet breathing of dry air. After a five minute period of deep breathing, however, it was elevated to 3,564 cc, a gain of 286 cc, or 8.7 per cent. The expected vital capacity was 3,915 cc. After the last part of the experiment, the râles were fewer, the costal margins were moving laterally throughout their entire extent with inspiration, and the lung bases were elevated 2 cm.

In this case moisture in the bronchi due to myocardial insufficiency caused emphysema. This in turn resulted in a decreased vital capacity and increase of lung volume. Breathing dry air decreased the lung volume, as shown by the position of the bases and the excursion of the costal margins.

Table 2 shows the results obtained in a series of cases, similar to those cited above, in which myocardial insufficiency was the cause of pulmonary edema, increased volume of the lung and diminished vital capacity. There was an average increase of 190 cc, or 11.4 per cent in vital capacity as a result of breathing dry air. The greatest increase was 484 cc, or 50.8 per cent, and the lowest figure was a decrease of 88 cc, or 8.3 per cent. Eighty-two per cent of the determinations showed an increase from 110 to 484 cc, 7 per cent less than 100 cc, and 11 per cent a decrease of less than 100 cc.

These results are to be contrasted with those of table 1. The conclusion seems warranted that breathing dry air extracted sufficient moisture from the bronchial tree to decrease the resultant emphysema. That emphysema was present could not be doubted when the movement of the costal margins before and after breathing dry air was observed. Emphysema, therefore, was one of the factors in the reduction of vital capacity, which was increased when the emphysema was decreased by extraction of moisture from the bronchi.

The foregoing results and conclusion are applicable only to patients who have emphysema caused by excessive moisture in the bronchial tree. In cardiac cases, with no signs of myocardial insufficiency except a lowered vital capacity, dry air should, theoretically, give no increase, and experimentally it does not. The decreased vital capacity in such cases is due to lung rigidity from engorged capillaries and interstitial edema. Therefore, since there is no excess of moisture in the bronchi, dry air can be of no value. Table 3 shows results in such cases. The average increase of vital capacity was 35 cc., or 1.3 per cent.

TABLE 2—*Decompensated Cardiac Cases*

Case	Gain or Loss of Vital Capacity After Dry Air,		Case	Gain or Loss of Vital Capacity After Dry Air,	
	Cc	Gain or Loss in Percentage		Cc	Gain or Loss in Percentage
1	+110	+ 7.2	25	+198	+13.4
2	+242	+11.3	27	+110	+11.9
3	+330	+14.0	29	+154	+25.0
4	+ 22	+ 1.1	30	- 44	- 4.0
8	+242	+12.1	32	+154	+ 5.6
9	- 44	- 2.7	36	+264	+ 7.7
17	+220	+12.8	38	+286	+11.4
	+ 66	+ 3.0	39	+198	+12.0
	+176	+ 8.4	41	+220	+11.4
18	+352	+24.2	42	+286	+ 8.7
19	+264	+23.1	43	+176	+ 4.5
20	- 88	- 8.3	49	+484	+52.3
21	+378	+13.7		+198	+20.4
24	+196	+ 7.2			

Several illustrative cases are given below.

CASE 6—F. M., aged 43, had a condition diagnosed as acute fibrinous pericarditis, acute myocarditis and auricular fibrillation.

On the day of the experiment there were no abnormal physical signs except an occasional râle at the lung bases. The expected vital capacity was 3,800 cc. Before and after the patient had breathed dry air, the vital capacity was 2,838 cc., and 2,882 cc., a gain of 44 cc., or 1.5 per cent.

The actual vital capacity in this case was about 1,000 cc. less than the expected capacity. There was little free moisture in the bronchial tree and no emphysema, as was shown by the normal excursion of the costal margins. Lung rigidity due to cardiac stasis and not to emphysema, therefore, was the cause of a decreased vital capacity. Since dry air could not affect the rigidity of the lung, it could likewise not affect vital capacity.

CASE 11—L. McL., aged 28, had a condition diagnosed as mitral stenosis and insufficiency.

There was a good state of cardiac sufficiency with the exception of a vital capacity of 1,870 cc., as contrasted with an expected vital capacity of 2,960 cc. After the patient had breathed dry air, the vital capacity was 1,848 cc., a loss of 22 cc., or 1 per cent.

The reduced vital capacity in this case was due to the same causative factor mentioned in case 6.

There is another type of case in which dry air should produce no change in vital capacity, namely, atrophic emphysema, and this probably accounts for failure to obtain an increase in certain cases of asthma of long duration. There are patients with asthma, however, who do respond with an increase of vital capacity, and who show objective and subjective change after dry air. Which patient will respond in this manner, and which will not is a matter of conjecture, but this makes the experiment of clinical value because it makes possible the classification of patients.

Those who respond favorably to a short test with dry air probably would find a climate with a lower relative humidity much more comfortable and less conducive to acute attacks. If all cases of asthma were due to free moisture in the bronchi, dry air would be of advantage.

TABLE 3—*Compensated Cardiac Cases*

Case	Gain or Loss of Vital Capacity After Dry Air, Cc	Gain or Loss in Percentage	Case	Gain or Loss of Vital Capacity After Dry Air, Cc	Gain or Loss in Percentage
5	0	0.0	15	+ 22	+0.8
6	+44	+1.5	16	+146	+5.9
7	+64	+1.0	18	0	0.0
10	+22	+0.8	28	+ 66	+1.6
11	-22	-1.0	41	+ 44	+1.5
12	0	0.0	46	0	0.0
	+66	+5.0	47	+ 44	+1.8
14	+22	+0.9			

to the entire group. However, there are cases with little moisture, as shown by few râles and minimal expectoration. The mechanism of bronchial obstruction in such cases is not clearly understood. It may be due to hypertonus of the bronchi according to the common conception or, according to a newer idea, to hives of the bronchial mucosa similar to those seen in the skin in protein sensitization.

The recent unpublished work of Hoover and Beams (Lakeside Hospital) proves that emphysema, as produced in guinea-pigs during anaphylaxis, is not caused by bronchiolar hypertonus, but by edema of the mucosa which produces wheals not unlike those seen in urticaria of the skin. This condition results in bronchial stenosis and emphysema.

Regardless of condition, whether it be hypertonus or hives, the fact remains that the obstruction in the bronchus is not free moisture and should not in any way be affected by breathing dry air. If there is a combination of both, dry air might be of some value. Accordingly, a number of patients with asthma were tested with dry air before and after the giving of epinephrine hydrochloride.

Cases 49, 50, 52 and 54 (table 4) amplify the foregoing discussion

TABLE 4—*Effect of Dry Air Before and After the Use of Epinephrine Hydrochloride in Asthma and Emphysema*

Case	Gain or Loss of Vital Capacity Before Epinephrine Hydrochloride, Cc	Gain or Loss in Percentage	Gain or Loss of Vital Capacity Due to Epinephrine Hydrochloride Cc	Percentage	Gain or Loss of Vital Capacity After Epinephrine Hydrochloride Cc	Gain or Loss in Percentage
1	0	0 0	+ 110	+ 7 7	+110	+ 7 2
13	0	0 0	+ 198	+ 12 0	+ 22	+ 1 2
22	+44	+ 1 5				
40	-110	- 6 0				
44	+178	+13 1				
49	+286	+31 0	0	0 0	+198	+18 0
50	0	0 0				
51	0	0 0				
52	- 44	- 1 6	+1 0 6	+ 39 1	+462	+12 5
53	+ 44	+ 4 1				
54	+260	+21 1	+1 588	+106 4	+418 +286	+13 6 + 8 3
55			+ 220	+ 10 8	+154	+ 4 7
56	0	0 0				

Table 5 shows the results obtained in several cases of pulmonary infiltration, but the results are too few for comment. It seems likely that further work will show an increase of vital capacity in resolving lobar pneumonia or a bronchopneumonia with considerable bronchial moisture.

TABLE 5—*Pulmonary and Pleural Conditions*

Case	Gain or Loss of Vital Capacity After Dry Air Cc	Gain or Loss in Percentage	Condition
26	+308	+12 8	Lobar pneumonia
31	0	0 0	Bronchitis
33	+ 44	+ 1 3	Lobar pneumonia
34	+110	+ 4 3	Pleurisy with effusion
35	+198	+ 8 8	Bronchopneumonia
37	- 44	- 1 8	Lung abscess
45	+176	+ 4 8	Pleurisy with pulmonary infiltration
48	+ 22	+ 0 9	Lobar pneumonia

#### ASTHMATIC CASES

CASE 49—J. K., aged 48, had a condition diagnosed as chronic emphysema, chronic bronchitis, chronic myocarditis and myocardial insufficiency.

This patient entered the hospital because of shortness of breath, edema of the legs, swollen abdomen and palpitation, all of which were of two weeks' duration. Asthma had been present for twelve years. On the day of the experiment, the examination showed a marked degree of cyanosis, the heart enlarged in all diameters, and poor motility of the lungs, as shown by diminished undulation and the mediastinal movement of the entire extent of both costal margins. The percussion note was tympanic throughout the chest, and there were many musical and bronchial râles.

The expected vital capacity was 4,225 and the actual 924. After the patient had breathed dry air for five minutes, the vital capacity was 1,210—an increase of 286 cc., or 31 per cent. The costal margins were now moving laterad throughout their entire extent, but there was no change in the number or character of the râles. The patient felt distinctly better. Ten minutes after

breathing the dry air, the patient's vital capacity was 1,122 cc, and the left lateral costal margin was stationary. After the administration of 7 mm of epinephrine hydrochloride, the vital capacity was 1,122 cc, and thirty minutes later it was 1,100 cc—there being no effect objectively or subjectively caused by the drug. Dry air was again used for ten minutes, and the vital capacity rose to 1,298 cc, an increase of 198 cc, or 18 per cent. Both costal margins were moving vigorously in the laterad direction, and there was further subjective improvement. This case showed a total increase of 484 cc, or 52.3 per cent, due entirely, therefore, to the breathing of dry air. A subsequent observation on the same patient showed the following. The vital capacity before and after the breathing of dry air was 924 and 1,034 cc, respectively, an increase of 110 cc, or 11.9 per cent. Dry air was now continued for another ten minute period which resulted in an elevation to 1,122 cc—a further increase of 88 cc, or 8.5 per cent. Thus there was a total increase in this instance of 198 cc, or 20.4 per cent. The costal margins which had been moving mediad before the experiment were now moving laterad.

In this case decreased vital capacity could have been due to myocardial insufficiency, bronchiolar hypertonus, bronchiolar edema, atrophic emphysema or a combination of these conditions.

Before the patient had breathed dry air, the costal margins were moving mediad with inspiration, indicating in the light of other physical observations, a low position of the diaphragm due to emphysema. After the breathing of dry air, both costal margins moved laterad with inspiration, indicating a lessening of the emphysema. An increased vital capacity also resulted. The conclusion can be drawn, therefore, that one factor causing a decrease of vital capacity was moisture in the bronchial tree which resulted in emphysema. The vital capacity was not affected to a greater degree because of atrophic emphysematous changes and rigidity from cardiac decompensation. After a ten minute interval, the vital capacity had dropped about 100 cc, and, what was more striking, the left lateral costal margin was now stationary on inspiration. The latter observation indicated an increase of emphysema of the left lower lobe as the result of a recurrence of moisture in that part of the bronchial tree. At this time, epinephrine hydrochloride gave no change of physical signs or vital capacity, therefore the emphysema was not due to bronchial hypertonus. The breathing of dry air then caused the left lateral portion of the costal margin to move laterad with inspiration. At a later date, the experiment was repeated with similar results.

Thus it may be concluded from this case that moisture in the bronchial tree caused emphysema and decreased vital capacity. Bronchiolar hypertonus contributed nothing to the decrease of vital capacity, but cardiac stasis and possibly atrophic emphysema contributed to a great degree. These factors could not be modified by dry air, therefore there was not a greater increase of vital capacity.

CASE 50—P. B., aged 42, had a condition diagnosed as allergic asthma.

Seven months prior to admission to the hospital, the patient had had an attack of what appeared to be hay-fever which later developed into a typical asthma. There had been several severe attacks since the onset. The expected vital capacity was 3,875 cc, and the actual 3,080 cc. At this time the patient was not having paroxysms, and there were no physical signs except a few musical râles in the chest. After the patient had breathed dry air for five minutes, the vital capacity remained the same, and there was no change as to râles or subjective improvement. A later determination during a paroxysm showed the vital capacity to be 1,800 cc before and after a ten minute period of breathing dry air. There were no more râles at this time, but the dry air

produced no change, and there was also no subjective improvement. A still later determination gave 1,562 cc before and after dry air, and this time there was a profusion of bronchial râles, restraint of lateral portion of the costal margin and a depression of the lung bases. The experiment accentuated unpleasant subjective symptoms. The administering of epinephrine hydrochloride gave almost instantaneous relief, but unfortunately the vital capacity was not secured at this time.

In this case bronchial obstruction was due to hypertonus or hives and not to moisture. As was to be expected, dry air gave no relief whereas epinephrine hydrochloride markedly changed physical signs and vital capacity.

CASE 52—J K, aged 50, had a condition diagnosed as asthma.

There were only a few musical râles in the lungs, and the motility of the chest was good at the time of the experiment. The expected vital capacity was 4,432 cc, and the actual 2,750 cc. After the patient had breathed dry air for five minutes, the vital capacity was 2,706 cc, a loss of 44 cc, or 1.6 per cent. After a further five minute period, it was 2,640 cc, a further loss of 66 cc, or 3.5 per cent. After the administration of 10 mm of epinephrine hydrochloride, the vital capacity rose to 3,690 cc, a gain of 1,056 cc, or 39.1 per cent. After full effect from the epinephrine hydrochloride, the vital activity remained at 3,696 cc, dry air was now breathed for five minutes, and the vital capacity rose to 4,158 cc, a further gain of 462 cc, or 12.5 per cent.

The reduction of vital capacity in this case was due to bronchial obstruction partly from moisture and partly from hypertonus. Dry air caused no change before epinephrine hydrochloride was injected, and it may be hypothesized that regional hypertonus prevented the dry air from reaching the bronchioles in which there was moisture. After full effect from the epinephrine hydrochloride, however, dry air gave a further gain of vital capacity. The additional hypothesis may be stated that when the regional hypertonus was removed by epinephrine hydrochloride, dry air penetrated to the bronchioles and removed moisture which still remained a partial cause of obstruction.

CASE 54—F F, aged 53, had a condition diagnosed as chronic bronchitis with emphysema and asthma.

Examination showed the costal margins to be moving mediad throughout their entire extent. The lung bases were at the twelfth rib in the midscapular line, and there were musical râles throughout the chest. The expected vital capacity was 4,275 cc and the actual only 1,232. After the patient had breathed dry air for five minutes, the vital capacity was 1,492 cc, a gain of 260 cc, or 21.1 per cent. There was considerable subjective but no objective change in the patient's condition. Ten minims of epinephrine hydrochloride was now given and six and one-half minutes later the vital capacity was 3,080 cc, a gain of 1,588 cc, or 106.4 per cent. There was no further increase six and one-half minutes later. The costal margins were now moving laterad throughout. The right base was elevated 3 cm and the left, 5 cm. All the râles with the exception of a few crepitant ones at the bases, had disappeared. There was, of course, marked subjective improvement. Dry air was now instituted for five minutes, and the vital capacity rose further to 3,498 cc, a gain of 418 cc, or 13.6 per cent. There were no further changes in the physical signs, but the patient felt better and resented the discontinuing of breathing dry air.

This case presents bronchial obstruction from a combination of hypertonus and moisture. Dry air increased the vital capacity by extracting a part of the bronchial moisture, epinephrine hydrochloride increased it markedly by relieving hypertonus, after which dry air was still further effective by penetrating bronchi in which moisture still produced a stenotic affect.

#### SUMMARY

1 An experimental method is described for testing the effect, on vital capacity, of breathing dry air.

2 One hundred patients, normal as to heart and lungs, were tested. The average increase of vital capacity in these cases was 12.5 cc or 0.3 per cent.

3 A number of patients with cardiac decompensation were tested, there was an average increase of 190 cc, or 11.4 per cent.

4 In patients with cardiac compensation there was an average increase of only 35 cc, or 1.3 per cent.

5 Patients with asthma varied in their response. Several responded with an increase before and after the injection of epinephrine hydrochloride. Others responded with an increase due to dry air and none to epinephrine hydrochloride, the response in others was just the reverse.

#### CONCLUSIONS

The conclusion seems justified that breathing dry air extracts enough of the moisture to increase temporarily the vital capacity in the majority of patients with bronchiolar edema, decrease the lung volume and number of râles and produce a sense of subjective relief. However, if the vital capacity is reduced because of bronchial obstruction other than moisture, interstitial pulmonary edema or a rigid lung due to stasis, breathing dry air causes no change. The procedure may also be used to differentiate between those patients with asthma whose bronchial obstruction is due chiefly to moisture and not to hypertonus or hives and thus will be selective of cases in which the patients will improve, in all probability, in a dryer climate.

# INTRAVENOUS INJECTION OF OUABAIN IN MAN\*

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AND  
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During the past five years, in the third medical (New York University) division of Bellevue Hospital, we have been making controlled observations on the preparations, dosage, absorption and evidences of disappearance of the digitalis bodies in patients suffering from organic heart disease. Studies have been made, in conjunction with Eggleston<sup>1</sup> and the Cornell medical division, on the absorption of digitalis when given by mouth, on the dosage and absorption of digitalis rectally administered and on the absorption and dosage of various preparations given hypodermically. We have found that absorption from the gastro-intestinal tract is so rapid and uniform, and when given in maximum dosage, complete digitalization takes place so promptly (within six to eight hours), that we have felt little practical need for giving the drug intravenously.

However every physician is confronted from time to time with patients who because of persistent vomiting due to the passive congestion caused by heart failure are unable to retain digitalis given by mouth. Such patients usually can be given digitalis by rectum but we have had experience with a few patients who were unable to retain the drug when it was given by this method. These patients are in need of digitalization, and one must resort to hypodermic medication. If the intravenous method is safe it would seem to be the method of choice because of its rapidity of action, and because there is no after-pain as is the case with subcutaneous or intramuscular injections.

Furthermore, it occurred to us that if the action of intravenous medication is as rapid as has been described it might be possible to give fractional doses at such short intervals that total digitalization could be produced rapidly. A comparison might be made as was done by Eggleston<sup>2</sup> (with digitalis by mouth), as to the dose required in relation to sex, age, cardiac condition and body weight. By the intravenous method these results should be more accurate as the variables of absorp-

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\* Read before the Section of Medicine, New York Academy of Medicine, April, 1926.

1 Eggleston, C., and Wyckoff, J. The Absorption of Digitalis in Man, *Arch Int Med* **30** 133 (Aug.) 1922.

2 Eggleston, C. Digitalis Dosage, *Arch Int Med* **16** 1 (July) 1915.

tion and elimination are greatly diminished. The end reaction also, namely, the point of complete therapeutic digitalization, should be more accurately determined, as it is possible to have the patient under continuous observation from the initial dose to the time of complete digitalization.

It was decided to use intravenously a preparation which was readily procurable and standard in its activity. Ouabain, which is amorphous strophanthin, otherwise known as strophanthin gamma, was the preparation decided on. Hatcher and Bailey<sup>3</sup> have shown it to be a standard preparation. Cohn and Levy<sup>4</sup> and others have described its activity on man. As in the case of other digitalis-like intravenous preparations, there is considerable divergence of opinion, however, as to its dosage. Hatcher and Bailey state that no more than 0.5 mg. should be given in twenty-four hours. Cohn and Levy, on the other hand, have given twice that amount (1.1 mg.) in two hours. Levine and Cunningham's<sup>5</sup> experiments showed the margin between the minimum toxic dose and the minimum lethal dose to be 48 per cent. Levine therefore, recommends that the drug be injected intravenously in small doses, 0.1 mg. every half hour, so that there will be no danger of giving an excess of more than 0.1 mg. of the minimum toxic dose; the sign of intoxication should be carefully watched for during the intervals between injection.

Cases of sudden death following the intravenous injection of all of the digitalis-like bodies have frequently been reported. Levine believes that such accidents may be avoided by the fractional method of dosage, particularly is this true if partial digitalization has been produced before the patients are given intravenous medication.

The reports of such cases of sudden death have made physicians wary as to the use of intravenous medication. In spite of this fact, Levine states that Vasquez and Luttenbacher have reported nearly 2,000 intravenous injections of ouabain without harm or fatality. On the other hand, Cohn and Levy,<sup>4</sup> giving ouabain at one hour intervals, the first dose being from 0.4 to 0.5 mg. and the second usually from 0.3 to 0.5 mg. found that ventricular premature contractions or ventricular paroxysmal tachycardia developed in 52 per cent of their patients with auricular fibrillation and in 12.5 per cent of the patients in whom there was regular sinus rhythm. When comparable doses of digitalis were given by mouth only one-half that percentage of toxic effects was noted.

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3 Hatcher, R. A., and Bailey, H. C. The Clinical Use of Strophanthus, *J. A. M. A.* **55**:1697 (Nov.) 1910.

4 Cohn, A., and Levy, R. A Comparison of the Action in Patients of G-Strophanthin and Digitalis, *Proc. Soc. Exper. Biol. and Med.* **17**: 81, 1919-1920.

5 Levine, S. A., and Cunningham, T. D., The Margin of Safety of Intravenous Digitalis in Cats, *Arch. Int. Med.* **26**: 293 (Sept.) 1920.

Cohn and Levy <sup>4</sup> state that it is rare for the dosage of ouabain used by them on patients with auricular fibrillation to decrease the rate of the ventricle for more than five days

#### EFFECT OF OUABAIN ON PATIENTS WITH ORGANIC HEART DISEASE

As in a cardiac service in which more than 300 patients with various degrees of heart failure are admitted every year, patients are occasionally seen who would be benefited by extremely rapid digitalization if it is safe, it was decided to make a study of the intravenous dosage of ouabain necessary to produce therapeutic effects, its action time and the time of the persistence of the action

For the purpose of studying the rate of absorption and total dose needed, patients having organic heart disease with auricular fibrillation were selected. These patients were put at rest in bed on a limited fluid intake and a uniform diet. Daily observations were made as to the ventricular rate, pulse rate, weight, water intake and urine output. The patients were observed in this way during a control period of from five to ten days. On the day on which ouabain was to be administered, observations of ventricular and pulse rates were made every five minutes (fig 1), previous to the first injections by about one hour. At the end of that time the initial dose of ouabain was administered intravenously, and the drug was administered every half hour until a full therapeutic effect was obtained.

The first ten patients were given 0.1 mg. every half hour, after that an initial dosage of 0.5 mg. was usually given, because we had determined that all adult patients needed a larger dose. In these cases this large initial dose was followed by smaller doses, usually 0.1 mg. every half hour.

A beginning effect was considered to have taken place when an injection was followed by a definite ventricular slowing which persisted. Full therapeutic effect was considered to have been obtained when the ventricular rate was slowed to 80 or below with obliteration of the pulse deficit.

No patients who had received digitalis within two weeks were given ouabain.

The preparation of ouabain used was that put up by Lilly and Co. in ampules containing 0.5 mg. in 2 cc. of solution, 0.1 mg. of this preparation equals one cat unit.

In all, 28 patients with auricular fibrillation, three with regular sinus rhythm and one with auricular flutter received 248 injections. Seven of these patients had a high temperature at the time they were examined. In analyzing our results of dosage, the patients with high temperatures have been studied separately from those with normal temperatures.

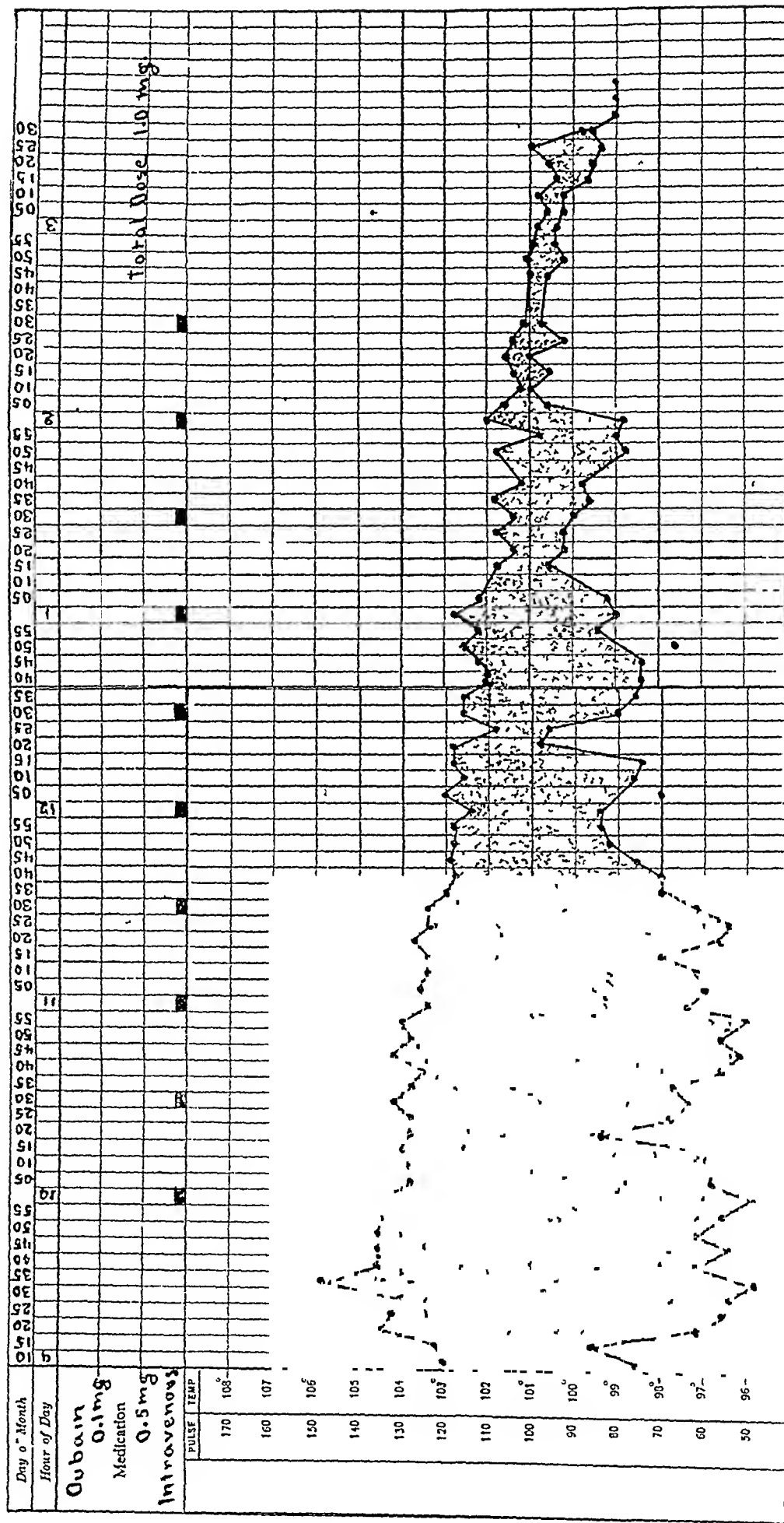


Chart 1 (Patient M C) —Observations made on ventricular and pulse rates on the day of injection, both during control period and after injection The diagnosis was acute rheumatic fever, enlarged heart mitral stenosis and insufficiency and auricular fibrillation

Table 1 shows the rapidity of action of ouabain given intravenously in auricular fibrillation. It will be seen that about one-half of the injections were followed by a beginning effect within five minutes and that all except four which showed any effect did so within fifteen minutes.

It was thought that there might be some relation between the size of the dose and the rapidity of action. Observations are arranged in

TABLE 1—*Rapidity of Action of Ouabain Given Intravenously in Auricular Fibrillation*

Total number of injections given	248
No effect noted (dose in all 0.25 mg. or less)	85
Effect noted in	163
Minutes After Injection Effect First Noted	Number of Cases
5	121
10	33
15	15
20	3
25	1

TABLE 2—*Relation of Size of Dose of Ouabain to the Rapidity of Action*

Size of dose in Mg.	Total Number of Experiments	Number of Experiments Showing Action	Number of Experiments Showing No Action	Minutes After Injection First Action Noticed (Average)	Minutes After Injection Greatest Action Noticed (Average)
0.5	21	21	0	5	25
0.4	3	3	0	5	21
0.25	47	37	12	8.2	18
0.2	23	17	6	5.8	13
0.1	154	86	68	7.1	10.5

TABLE 3—*Dosage in Mg. of Ouabain in Patients Without Elevation of Temperature*

Experiment Number	Mg. of Ouabain	Weight	Mg. Ouabain per Pound Body Weight	Experiment Number	Mg. of Ouabain	Weight	Mg. Ouabain per Pound Body Weight
1	0.8	149	0.0053	12	1.0	145	0.0051
2	1.0	149	0.0067	13	1.0	121	0.0082
3	1.1	149	0.0073	14	0.8	119	0.0067
4	1.7	187	0.0053	15	1.0	161	0.0062
5	0.7	210	0.008	16	0.85	160	0.0053
6	1.1	100	0.007	17	0.7	120	0.0058
7	1.1	123	0.0089	18	0.9	145	0.0062
8	0.95	123	0.0089	19	0.7	109	0.0064
9	0.95	148	0.0064	20	0.8	150	0.0073
10	1.0	133	0.0071	21	1.05	125	0.0084
11	0.75	133	0.0075				
Average dose per patient				0.95 mg.			
Smallest dose per patient				0.7 mg. or 26.8% below average			
Largest dose per patient				1.7 mg. or 78.9% above average			
Average dose in mg. per pound of weight				0.0067 mg.			
Smallest dose in mg. per pound of weight				0.0053 mg. or 20.9% below average			
Largest dose in mg. per pound of weight				0.0089 mg. or 32.8% above average			

table 2 so as to study such correlation. It will be seen that, as a rule, in patients receiving larger dosage, beginning action occurs more rapidly, but that it takes a longer time for full action of such a single dose.

Table 3 is arranged to show the dosage of ouabain in the patients without a rise in temperature. The weight noted in this table was the

weight of the patient free from edema. Regardless of body weight, it will be seen that the average dose per patient is 0.95 mg. The smallest dose which produced full therapeutic effect was 0.7 mg or 26.3 per cent below the average dose. The largest dose needed by any patient was 1.7 mg or 78.9 per cent above the average.

In terms of milligrams of ouabain per pound weight the average was 0.0067 mg. The smallest dose was 0.0053 mg or 20.9 per cent below the average, and the largest dose was 0.0089 or 32.8 per cent above the average.

This would appear to bear out Eggleston's<sup>2</sup> statement that there is a distinct relationship between body weight and the amount of digitalis body necessary to produce a therapeutic effect.

Table 4 shows the same figures in seven patients having a rise in temperature. The average dosage both per patient and per pound body

TABLE 4—*Dosage in Mg of Ouabain in Patients with Elevation of Temperature*

Experiment Number	Mg of Ouabain	Weight	Mg Ouabain per Pound Body Weight	Experiment Number	Mg of Ouabain	Weight	Mg Ouabain per Pound Body Weight
1	1.5	138	0.011	5	1.0	90	0.011
2	1.55	160	0.010	6	1.55	139	0.011
3	1.25	149	0.0083	7	1.0	105	0.0095
4	1.0	94	0.0106				
Average dose per patient				1.23 mg			
Smallest dose per patient				1.0 mg or 18.7% below average			
Largest dose per patient				1.55 mg or 25.2% above average			
Average dose in mg per pound of weight				0.01 mg			
Smallest dose in mg per pound of weight				0.0083 mg or 17.8% below average			
Largest dose in mg per pound of weight				0.011 mg or 8.9% above average			

weight was higher than in the patients with no elevation in temperature. The average dosage per patient was 1.23 mg, and the average dose in mg ouabain per pound body weight was 0.01 mg. The smallest dose in this series which produced therapeutic effect was 1 mg or 18.7 per cent below the average; the largest was 1.55 mg or 25.2 per cent above the average.

The variations above and below the average in terms of milligrams of ouabain per pound body weight were 0.0083 mg or 17.8 per cent below and 0.011 or 14.9 per cent above the average. In this small series the total dose per patient would seem to have no particular relationship to weight.

It was decided to determine whether it is possible to determine the rate of elimination or destruction of ouabain from the body. For this purpose after periods varying from two to nine days ouabain was again administered intravenously, usually 0.1 mg every half hour until the ventricular rate had been brought down to a point approximately the same as after the first full effect (fig. 2).

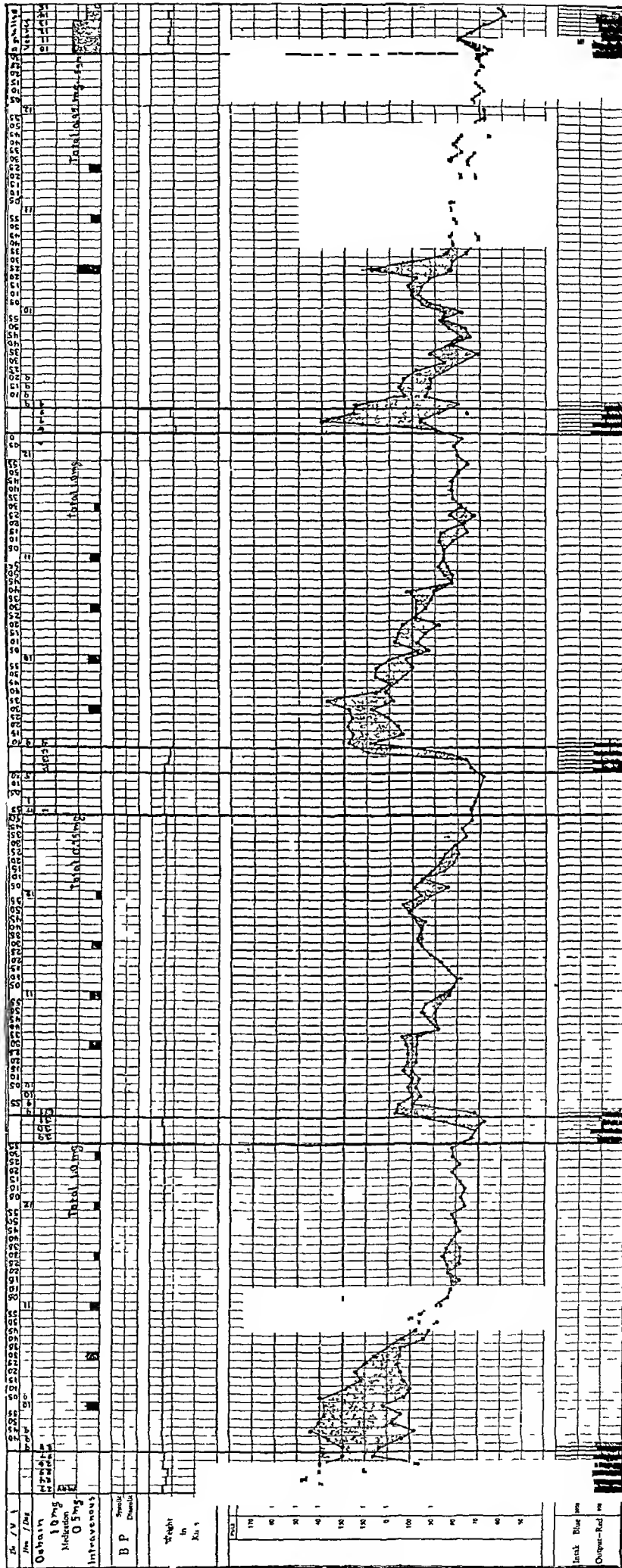


CHART 2 (Patient F W) —The type of observations made in order to determine persistence of ouabain action The diagnosis was acute rheumatic fever, enlarged heart mitral stenosis and insufficiency and auricular fibrillation

Table 5 shows the amount of ouabain needed to produce an effect similar to the effect of the initial dosage. This is shown both in milligrams of ouabain and in percentage of the initial dose. A study of this table shows a marked difference in the rate of elimination. It would seem that the drug is eliminated more rapidly during the first two or three days. There are other patients who seem to eliminate the drug more slowly, if this method can be relied on to show elimination.

TABLE 5—*Studies in Elimination or Destruction of Ouabain*

Initial Dose, Mg	Number of Days After Full Dosage Drug Resumed	Amount Needed to Produce Effect Similar to Effect of Initial Dosage, Mg	Estimated Elimination Rate in 24 Hours, Mg	Percentage of the Initial Dosage
1.55	2	0.95	0.47	61.3
1.0	2	1.0	0.5	100.0
1.7	2	1.0	0.5	58.8
1.7	2	1.0	0.5	58.8
0.8	3	0.35	0.117	43.5
0.8	3	0.55	0.163	68.5
0.95	3	0.6	0.2	63.2
1.0	4	1.0	0.25	100.0
1.0	4	1.0	0.25	100.0
1.0	4	1.0	0.25	100.0
0.95	4	0.95	0.24	100.0
1.0	4	0.5	0.125	50.0
1.0	4	0.5	0.125	50.0
0.7	4	0.5	0.125	71.4
1.55	4	1.35	0.34	87.7
0.95	5	0.85	0.17	89.4
1.0	5	0.7	0.14	70.0
0.95	6	1.0	0.16	105.0
1.0	7	0.7	0.1	70.0
1.0	9	0.85	0.093	85.0

TABLE 6—*Persistence of Action of Ouabain After Full Therapeutic Effect*

Amount of Initial Dosage in Mg	Duration of Persistence of Action in Days	Amount of Initial Dosage in Mg	Duration of Persistence of Action in Days
0.65	1	0.7	4
0.5	1	0.7	4
		0.95	4
0.65	2	1.0	4
		1.55	4
0.8	3		
0.8	3	0.75	5
1.0	3		
1.05	3	0.7	9
1.05	3		

As we thought that the persistence of the action of ouabain might be an indication to the excretion of the drug, fifteen cases were studied after the initial dosage until all effects had disappeared. Table 6 shows the results of this study. While it again shows a wide variation, all except one of the patients showed that the action of the drug had disappeared at the end of five days. This is in accordance with the work of Cohn and Levy.<sup>4</sup>

Besides making these observations on the effect of ouabain on patients with auricular fibrillation, we treated with intravenous injections of ouabain three patients who had regular sinus rhythm, one patient was given a total of 0.8 mg in three doses of 0.5 mg, 0.2 mg and 0.1 mg given one hour apart. A second patient was given 0.9 mg in doses of 0.5 mg, 0.2 mg and 0.2 mg at one hour intervals. A third patient was given 0.5 mg in five doses of 0.1 mg each at intervals of one hour. All three of these patients showed marked clinical improvement. Hourly electrocardiograms were taken in these cases, but no definite increase in the P-R interval, and no marked or permanent T wave changes were noted. This also is in accordance with the observations of Cohn and Levy.<sup>4</sup>

One patient who had auricular flutter with 2:1 block received 1.25 mg in four doses of 0.5, 0.25, 0.25 and 0.25 mg at one hour intervals. This resulted in an increase of the 2:1 auricular ventricular block to 4:1 block, but there was practically no change in the rate of flutter, though the patient vomited. It was considered inadvisable to continue the administration of ouabain, all medication was stopped for six days, 2:1 block again returning. Digitalization was then produced by mouth, the patient receiving 13 cc of a standardized tincture of digitalis or 0.1 of a cat unit per pound body weight in a single dose. The next day he was given 6 cc more making a total dosage of 19 cc or 0.15 of a cat unit per pound body weight. The auricular flutter persisted with varying block. Two days later he was given 7 cc of digitalis, making a total of 26 cc or 0.2 cat unit per pound body weight, flutter persisted for forty-eight hours then fibrillation suddenly set in without further digitalization.

In our series full therapeutic digitalization was produced fifty-two times in thirty-two different patients. One patient developed premature ventricular contractions, two patients developed vomiting. No other toxic symptoms were noted. There were no fatalities.

#### SUMMARY

Two hundred and forty-eight intravenous injections of ouabain were administered to thirty-two patients who had heart failure without fatalities or harmful effects.

One hundred and sixty-three of these injections were followed by a definite cardiac effect. The initial effect was noted in from five to twenty minutes and the maximum effect in from fifteen to fifty minutes, as a rule, the larger the dose the earlier the initial effect and the more delayed the maximum effect.

A greater amount of ouabain was necessary to reduce the ventricular rate in patients who had auricular fibrillation with elevation of temperature than in those without elevation of temperature.

The variation in dosage was less when calculated on the basis of body weight than on the basis of total dosage.

The persistence of action of the drug was variable in the cases observed, but in all except three the persistence was never longer than five days

Mild toxic symptoms were noted in three of fifty-two instances in which full therapeutic effects were obtained

It would seem that ouabain, if given in fractional doses, may be administered with safety intravenously to patients with auricular fibrillation that have not received digitalis recently

When ouabain is given to patients with regular sinus rhythm, greater care must be used. In these patients clinical improvement seems to be the only criterion for full therapeutic effect, and since moribund patients may not show clinical improvement, there is greater danger of overdosage

# HOUSE DUST IN THE ETIOLOGY OF BRONCHIAL ASTHMA AND OF HAY-FEVER \*

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House dust sensitization has gained increasing recognition in the etiology of bronchial asthma and hay-fever during the last four years. Hay, grain and feed dusts as well as dusts with which bakers, millers, wood workers and other artisans come in contact may also cause marked symptoms. However attention in this article will be focused on house dusts that are the most important of this group.

## LITERATURE

Kern <sup>1</sup> in 1921 first called attention to house dust sensitization, especially to the dust of bedrooms. He felt that many patients diagnosed by Walker as having nonsensitive asthmatic bronchitis were probably sensitive to house dust. He recommended routine tests with dust extracts especially in cases in which other skin tests were negative.

Cooke <sup>2</sup> in 1922 published his observations on house dust sensitization. He reported a case of asthma of fourteen years' duration in a man aged 26, who gave no positive skin reactions except to dust extracts, and whose asthma was entirely controlled by eliminating the offending dust from his environment. Of 327 patients with asthma, 109 were found sensitive to his stock dust <sup>1</sup>. Cooke predicted that dust extracts would be of definite diagnostic value in discovering etiologic substances in the environment of the patient. He felt that the active principle in dust was possibly a new, specific and unknown one.

Spivacke and Grove <sup>3</sup> in 1925 substantiated Cooke's idea that house dust contains a specific substance, rather than some common inhalation protein such as that of horse dander. They felt, however, that there are many different dust atopens.

Grove and Coca <sup>4</sup> in 1925 found the ability of house dust and pollen extracts to give skin reactions unchanged after the probable removal of all nitrogenous substances by dialysis and tryptic digestion. From

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Read before the American Association for the Study of Allergy, Dallas, Texas, April 18 1926

1 Kern, A. Dust Sensitization in Bronchial Asthma, *M Clin N Amer* **5** 751 (Nov) 1921

2 Cooke, R. A. New Etiologic Factors in Bronchial Asthma, *J Immunol* **7** 147-162 (March) 1922

3 Spivacke, C. A., and Grove, E. F. A Study of House Dust Atopen in Asthma, *J Immunol* **10** 465-469 (March) 1925

4 Grove, E. F. and Coca, A. F. A Study of the Atopens of Pollen, House Dust, Horse Dander and Green Pea, *J Immunol* **10** 471 (March) 1925

such data they concluded that the active principle of dust and pollen extracts was not a protein and that of horse dander and green pea extracts was a protein

Black<sup>5</sup> stated in 1926 that tolerance to the active principle of pollen can be obtained with apparently protein free extracts

Alles,<sup>6</sup> however, feels that it is nearly impossible to be sure that a biologic solution contains no protein

Brown<sup>7</sup> reported 47 reactions to dust extracts out of 100 patients with asthma

Meyer<sup>8</sup> in 1923 reported 57 per cent of 235 asthmatic patients sensitive to dust extracts. Of sixty-one dust extracts tested, fifty-five gave positive skin reactions. He felt that house dust is the most common cause of bronchial asthma

In 1925, Leopold<sup>9</sup> demonstrated the specific effect of house dust on patients with asthma who were sensitive to such dust. This work was carried out in a dust proof room in which the temperature, humidity and the type of dust in the air were under absolute control

## HISTORY

Patients will frequently give the history of coughing or sneezing or of hay-fever or asthma when in an atmosphere filled with house dust. One man with constant asthma for fourteen years dated his trouble from beating a carpet. Such patients avoid sweeping and cleaning knowing that they are more comfortable if the dust is not disturbed. One college professor discovered that if his room was never cleaned and the windows never opened he was able to use it with the minimal coughing and sneezing. When cleaning was done he had to absent himself from his room for several days.

Dust sensitization is so marked in many patients that they have symptoms from the small amount that is at all times suspended in the air of the ordinary home. Such patients will sneeze or cough if in a draught that raises dust in the air. I feel that certain asthmatic patients who develop asthma a few hours after returning are probably sensitive not only to feather or other emanation proteins but also to the dust of their bedroom which gradually accumulates on the mucous mem-

5 Black, J. H., and Moore, M. C. Pollen Therapy with Protein-Free Extracts, *J. A. M. A.* **86** 324-325 (Jan. 30) 1926

6 Alles, G. A. Pollen Therapy with Protein-Free Extracts, *J. A. M. A.* **86** 1151 (April 10) 1926

7 Brown, A. Present Day Treatment of Asthma, *New York M. J.* **118** 333, 1924

8 Meyer, G. P. House Dust in Asthma, *Atlantic M. J.* **27** 59-61 (Nov) 1923

9 Leopold, S. S., and Leopold, C. S. Bronchial Asthma. A Study Under Controlled Conditions of Environment, Temperature and Humidity, *J. A. M. A.* **84** 731-734 (March 7) 1925

branes until enough absorption occurs to cause symptoms. Such an explanation may be the real basis of the sneezing and coughing on arising from sleep. Dust sensitive patients are worse in the winter when they are confined more closely to their homes.

In my series of patients giving reactions to house dusts, 66 per cent gave histories suggesting such sensitization. It was noteworthy that men and children rarely gave such histories, probably because of lack of observation on their part.

HOUSE DUSTS AND THEIR EXTRACTS

House dust arises chiefly from materials of animal epidermal origin which furnish the home. Of these, feather pillows, hair mattresses, woolen blankets and carpets give rise to surprising amounts of dust.

TABLE 1—*Reactions to Proteins in Ten Patients with Asthma Sensitive to Stock Dust 13.\**

Case	Reactions to												
	Dust 13	Wheat	Eggs	Milk	Vegetable	Fruit	Spring Pollen	Fall pollen	Orris	Feathers	Horse	Cat	Sheep
1	+++	0	0	0	0	0	0	0	0	+	+	0	0
2	++++	0	0	0	0	0	++	0	+	++	+	0	0
3	++++	++	0	+	0	0	++	0	0	++	0	0	0
4	++++	0	0	0	+	+	++	0	0	++	0	0	0
5	++++	0	0	0	0	+	+	+	0	+	+	0	0
6	++++	0	0	0	+	+	0	0	0	+	+	0	0
7	++++	0	0	0	0	0	0	0	+++	++	++	0	0
8	++	0	0	0	0	+	+++	+++	++	+++	+++	0	+
9	+	0	0	++	0	0	+++	++	0	++	+++	+	+
10	++	0	0	0	0	0	+++	0	0	++	+++	0	0

\* Protein tests are reported in groups and in my routine tests have not been included.

House dust may also contain rabbit and goat hair from upholstery or from face powder, pyrethrum, glue, certain wood and matting dusts, as well as many others peculiar to each environment. To any of these the allergic person may become sensitive. Cooke feels, however, that house dust contains a specific substance that has no relation to any of these obvious sources of dust. He supports this opinion by a table of reactions to other common proteins in dust sensitive patients which shows that patients reacting strongly to the same dust exhibit no uniformity in their reactions to other inhalant or food proteins.

I have indicated in table 1 the cutaneous reactions obtained with the routine testing of patients sensitive to the most active dust (dust 13). These data show no regularity in the skin reactions obtained in the various patients, though all but two gave reactions to proteins of feathers and horse dander and all but three reacted to pollen extracts.

The last three cases are of interest since they gave marked reactions to proteins or animal emanations and pollens and less active results with the dust extract. In general the multiplicity of types and number of sensations and the dissimilarity of skin reactions in allergic patients are illustrated. These results seem to support Cooke's idea of a new specific principle in house dust about the ultimate proof of which I am doubtful.

The patient sensitive to house dust must live in an environment entirely free from the dust as well as from other substances to which he gives reactions. From clinical experience it must be assumed that the susceptible person can have symptoms at the slightest amount of the dust suspended in the air or his home. The degree of such sensitization

TABLE 2.—*Reaction of Patient to Various Extracts*

		EXTRACTS									
		Dust		Cat		Horse		Dog		Pollen	
		1	2	1	2	1	2	1	2	1	2
1	2	0	0	0	0	0	0	0	0	0	0
2	3	0	0	0	0	0	0	0	0	0	0
3	4	0	0	0	0	0	0	0	0	0	0
4	5	0	0	0	0	0	0	0	0	0	0
5	6	0	0	0	0	0	0	0	0	0	0
6	7	0	0	0	0	0	0	0	0	0	0
7	8	0	0	0	0	0	0	0	0	0	0
8	9	0	0	0	0	0	0	0	0	0	0
9	10	0	0	0	0	0	0	0	0	0	0
10	11	0	0	0	0	0	0	0	0	0	0

0 = no reaction; 1 = slight; 2 = moderate; 3 = severe; 4 = very severe.

must be very great. Also, Cole, Bock and Holmes in 1926 demonstrated that typical anaphylactic reactions occurred in a guinea pig when injected with a spray of the antigen which comparatively attains the important place of inhalants in the cause of asthma and hay fever.

The extracts of house dust used here have been prepared by extracting two or three amount of such dust with the same extracting fluid, allowing two days at ordinary temperature for each extraction. For some months Coccidi's extracting fluid was used, but for the last eight months 0.5 per cent sodium borate is suggested by Pinness. This gives a large number of active extracts. Such solutions have been sterilized by the addition of 0.3 per cent cresol and by Berkefeld filtration. Dust extracts have been prepared during the last year from dust from the houses of thirty

(9) Pinness, G. J., Miller, H. and Miles, G. A.: Comparative Method for Protein Extraction. *J. A. M. A.* 83: 608-611 (Apr. 25) 1924.

The first three cases are of interest since they give a broad picture of the proteins in animal excretions and indicate that these excretions with the dust extract. In general the molecular weights and number of sensitizations and the dissimilarity of skin reactions in allergic patients are illustrated. These results seem to support Coombs' idea that the specific principle in house dust above the ultimate point at which it no longer is doubtful.

The patient sensitive to house dust, must live in an environment entirely free from the dust as well as from other substances to which he gives reactions. I find chemical experience must be assumed that the susceptible person can have symptoms from the slightest amount of that dust suspended in the air of his home. The efficacy of such sensitization

TABLE 2—*Continued*

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

[illegible]

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The extracts of house dust have been prepared by extracting two or three amounts of such dust with the same extracting fluid allowing two days at ordinary temperature for each extraction. For some months Coca's extracting fluid was used but for the last eight months 0.5 per cent salt solution is suggested by Price. I gave a large number of active extracts. Such solutions have been sterilized by the addition of 0.3 per cent cresol or by Barthelemy's method. Dust extracts have been prepared during the last year from dust from the houses of 1213-

The last three cases are of interest since they gave mixed reactions to proteins of animal emanations and pollens and less active results with the dust extract. In general the multiplicity of types and number of sensitizations and the dissimilarity of skin reactions in allergic patients are illustrated. These results seem to support Cooke's idea of a new specific principle in house dust about the ultimate proof of which I am doubtful.

The patient sensitive to house dust must live in an environment entirely free from the dust as well as from other substances to which he gives reactions. From clinical experience it must be assumed that the susceptible person can have symptoms from the slightest amount of that dust suspended in the air of his home. The delicacy of such sensitization

TABLE 2—*Reactions of Patients to Their Own and Other Stock Dust Extracts\**

Case	Dusts Extracts*									
	1	2	3	4	5	6	7	8	14	16
1	<u>0</u>	<u>0</u>	—	—	<u>0</u>	<u>0</u>	—	—	—	<u>0</u>
2	<u>0</u>	<u>0</u>	0	—	—	0	—	—	0	0
3	0	0	<u>0</u>	—	—	—	—	—	—	0
4	+	+	0	<u>++</u>	0	—	+	—	+	0
5	0	0	0	+	<u>0</u>	0	0	0	0	0
6	0	—	—	—	—	<u>—</u>	0	—	—	—
7	0	0	0	0	0	0	<u>0</u>	—	—	0
11	0	+	0	0	0	0	—	<u>+</u>	—	0
14	—	+	0	0	0	0	—	0	—	0
16	0	0	0	0	0	0	0	0	0	—
19	0	0	0	0	0	0	0	0	0	<u>0</u>

\* The reaction to the patient's own dust is underlined. — indicates that no test was made.

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The extracts of house dust used have been prepared by extracting two or three amounts of such dust with the same extracting fluid, allowing two days at ordinary temperature for each extraction. For some months Coca's extracting fluid was used but for the last eight months 0.5 per cent salt solution as suggested by Piness<sup>10</sup> has given a large number of active extracts. Such solutions have been sterilized by the addition of 0.3 per cent cresol and by Berkefeld filtration. Dust extracts have been prepared during the last year from dust from the houses of thirty-

<sup>10</sup> Piness, G. Miller, H. and Allen, G. A. Comparative Methods of Protein Extraction. *J. A. M. A.* **83** (98-111) Vol. 23, 1924.

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2	++++	0	0	0	0	0	++	0	+	+	+	0
3	++++	++	0	0	0	0	++	0	0	+	0	0
4	++++	0	0	0	+	+	+	0	0	0	0	0
5	++++	0	0	0	0	0	+	+	0	+	+	0
6	++++	0	0	+	+	+	0	0	0	+	+	0
7	++++	0	0	0	0	0	0	0	++	+	+	0
8	++	0	0	0	0	+	+++	+++	+	+++	+++	+
9	+	0	0	++	0	0	++	0	0	+++	+++	+
10	++	0	0	0	0	0	+++	0	0	++	+++	0

\* Protein tests here reported in groups and many routine tests have not been included

House dust may also contain rabbit and goat hair from upholstery, oil from face powder, pyrethrum, glue, certain wood and matting dusts, as well as many others peculiar to each environment. To any of these, the allergic person may become sensitive. Cooke feels, however, that house dust contains a specific substance that has no relation to any of these obvious sources of dust. He supports this opinion by a table of reactions to other common proteins in dust sensitive patients which shows that patients reacting strongly to the same dust exhibit no uniformity in their reactions to other inhalant or food proteins.

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	1	2	3	4	5	6	7	11	14	16	10
1	0	0	—	—	D	D	—	—	—	—	0
2	D	D	0	—	—	0	—	+	0	0	0
3	0	0	0	—	—	—	—	—	—	—	0
4	—	—	0	+++	0	—	+++	+++	+	+	0
5	0	0	0	++	0	0	0	0	0	0	—
6	0	—	—	—	—	—	0	—	—	—	0
7	0	0	0	0	0	0	0	—	—	—	0
11	0	+	0	0	0	0	+	+++	+	—	0
14	++	+	0	0	0	0	—	0	+	—	0
16	0	0	0	0	0	0	0	0	0	+++	0
10	0	0	0	0	0	0	0	0	0	0	0

\*The reaction to the patient's own dust is underlined. — indicates that no test was made.

must be very great. Alexander Becke and Holmes in 1926 demonstrated that typical anaphylactic reactions occurred in sensitive animals who inhaled a spray of the antigen, which experimentally affirms the importance of inhalants in the cause of asthma and hay-fever.

The extracts of house dust used have been prepared by extracting two or three amounts of such dust with the same extracting fluid, allowing two days at ordinary temperature for each extraction. For some months Coca's extracting fluid was used, but for the last eight months 0.5 per cent salt solution as suggested by Pmess,<sup>10</sup> has given a large number of active extracts. Such solutions have been sterilized by the addition of 0.3 per cent cresol and by Berkefeld filtration. Dust extracts have been prepared during the last year from dust from the houses of thirty-

<sup>10</sup> Pmess, G., Miller, H., and Alles, G. A. Comparative Methods of Protein Extraction, J. A. M. A. 83: 608-611 (Aug. 23) 1924.

two patients with hay-fever or asthma. Twenty of these have given good skin reactions and have been kept for stock solutions. Table 2 details the reactions of ten such patients to their own dust extract and to the extracts of each of the other nine patients. This table indicates that in those cases in which no skin reactions to any dust extract were obtained and in which a definite history of dust sensitization was present we probably did not extract the dust from the proper rooms of the patient's house. This also applies in those cases in which reactions occurred to other dust than their own. Case 4 gave large reactions to several dust extracts including the autogenous one. Patient 16, however, gave no reactions except to her own extract. All of this supports the probability that house dust contains many, though possibly specific active principles.

#### SKIN TESTING

The skin testing with dust extracts, as well as with other proteins, has been done with the scratch method. I found that active dust extracts give good skin reactions with this method in many cases as large as the average pollen reaction. This report of the ability to obtain good reactions by the scratch method with dust extracts is the first definite one in the literature to date. The intradermal test, as recommended by Cooke, was used in the early testing with dusts, but I came to the conclusion that the scratch test gave as satisfactory evidence of dust sensitization. The absence of all constitutional reactions, the ease and rapidity of testing and the ability to test a patient with at least fifty proteins at a sitting, make me a strong advocate of the scratch method. In this work, the retesting of certain patients who fail to give expected reactions to dust extracts has resulted in positive reactions. As stated in previous articles these skin reactions have been interpreted as positive when an erythema or an irregular wheal larger than the control reaction is present. I feel that not all reactions indicate etiologic factors in the allergic problem of the patient, but that such reactions must be considered in the treatment until contrary proof is forthcoming.

#### BRONCHIAL ASTHMA

During the last year I have tested 160 new patients with asthma in my private work, with stock house dust solutions. Positive reactions to their own, or more often to stock, dust extracts have been found in seventy-three of this group. Thus 45 per cent of my series gave dust reactions as compared with 47 per cent reported by Brown and 57 per cent by Meyer. My stock dust 13 gave positive reactions in 36 per cent of 122 patients tested, which compares with the reactions obtained by Cooke in 31 per cent of 327 cases tested with his dust 1.

The results of the routine testing of seventy of these dust sensitive asthmatic patients, with usually more than 200 common proteins, are

given in table 3. These data are presented for comparison in the same form as were similar data in a series of 234 patients<sup>11</sup> with asthma in all ages and 110 patients<sup>12</sup> with asthma in childhood and in young adult life, published in 1925.

The data given in table 3 show that this group of dust sensitive patients gave about the same relative number of skin reactions to foods as did patients in the two previous series. The percentage of patients reacting to total animal proteins and particularly to the feather, horse dander and sheep wool proteins is much higher. The percentage of pollen sensitive patients in this series is higher by 20 per cent than in my previous series. These results are probably due to the fact that I was dealing with asthmatic patients all of whom were sensitive to inhalant dust proteins and all of whom gave skin reactions. The fact that 69 per cent of these

TABLE 3—Occurrence of Skin Reactions in Seventy Dust Sensitive Patients With Bronchial Asthma

Food Proteins	Patients Giving Reactions		Inhalant Proteins	Patients Giving Reactions	
	Number of	Per Cent		Number of	Per Cent
Wheat	15	21	Dust	70	100
Corn	0	0	Feathers	47	67
Oats	5	7	Horse	28	41
Rice	0	0	Cat	10	15
Egg	7	10	Rabbit	14	20
Milk	7	10	Sheep	17	22
Fish	6	9	Silk	7	10
Nuts	2	3	Miscellaneous	23	34
Meats	2	3	Total animal	55	82
Fruits	7	10	Orchard	8	12
Vegetables	16	23	Tree pollens	7	10
Beverages	2	3	Spring pollens	36	53
Spices	1	1	Fall pollens	24	35
Total food	81	46	Total pollens	42	62

dust sensitive asthmatic patients reacted to feather proteins 41 per cent to horse dander protein 26 per cent to rabbit fur protein and 22 per cent to sheep wool protein and the fact that other animal emanation proteins gave many reactions make me feel that their reactions to house dust might be due to dusts arising from certain articles of furnishing rather than from some unknown source, as suggested by Cooke. The frequency of pollen reactions suggests that certain house dusts may contain pollen. In fact the dust reaction might be a summation one due to slight sensitizations to various animal emanations, pollens or other substances present in the same dust extract.

The frequency of skin reactions to ten different house dust extracts in this series of seventy patients with asthma, as well as in a group of twenty patients with perennial hay-fever, is recorded in table 4. From this

11 Rowe, A. H. The Treatment of Bronchial Asthma, J. A. M. A. 84 1902-1905 (June 20) 1925.

12 Rowe, A. H. Bronchial Asthma in Children and Young Adults, Am. J. Dis. Child. 31 51-57 (Jan.) 1926.

table it is evident that certain dust extracts are more active in producing skin reactions than others. Out of this series of ten dusts, numbers 4, 13, 14 and 16 gave a high percentage of positive results. As pointed out before in table 2, however, no one stock dust gives reactions in all dust sensitive patients. This indicates the necessity of using a number of active dust extracts and autogenous extracts, when indicated in the study of the patient with a history of susceptibility to house dust.

The relative occurrence of dust sensitization according to age groups in these series of patients is recorded in table 5. It is especially interesting that 21 per cent of the patients with asthma were under 10 years of

TABLE 4—*Percentage of Positive Reactions to Ten Different House Dust Extracts*

Dust Extract	Seventy Cases of Asthma			Twenty Cases of Hay Fever		
	Number of Reactions	Number of Patients Tested	Percentage Giving Positive Reactions	Number of Reactions	Number of Patients Tested	Percentage Giving Positive Reactions
1	30	61	49	5	17	29
2	23	61	38	4	16	25
3	4	65	6	3	17	18
4	37	67	55	10	18	55.5
5	15	61	24.5	6	19	31.5
6	22	63	35	4	19	21
7	15	36	42	4	18	22
13	45	58	78	8	18	44
14	34	53	64	6	17	35
16	23	44	52	3	17	18

TABLE 5—*Percentage of Dust Sensitive Patients with Asthma and Hay-Fever in Various Age Groups*

Age Groups (Years)	Seventy Cases of Asthma		Twenty Cases of Hay Fever	
	Number of Cases	Per Cent	Number of Cases	Per Cent
0-10	15	21	5	15
10-20	10	14	2	10
20-50	37	53	14	70
50-80	8	11	1	5

age. The occurrence of dust sensitization in childhood and in youth, as well as in old age, is definitely reported for the first time in this table. It shows the importance of such sensitization and that no age is immune.

#### PERENNIAL HAY-FEVER

The patient who has slight or severe symptoms of hay-fever throughout the year always has been a problem for the specialist. Walker, in 1918, emphasized the importance of bacterial infection of mucous membranes as a cause of this trouble. In my experience, such bacterial infection, in the absence of sinusitis, is rarely the sole cause of coryza. Sinusitis especially of the antrum, may cause symptoms suggesting hay-fever, but the absence of allergy in the family and personal history, and the absence of itching and sneezing and of skin reactions, would

indicate the absence of bacterial sensitization as a cause for nasal congestion. Sinusitis complicating allergic hay-fever may at times require surgery for relief. Vaccine therapy probably helps to increase resistance to such infection.

In patients who had perennial hay-fever, routine testing with stock and autogenous house dust extracts has demonstrated that dust reactions frequently occur in such patients and the definite importance of house dust in the etiology of this condition. I have tested such patients routinely with the proteins of all common foods, animal emanations, pollens, orris root, and with several active dust extracts. The results of the testing of twenty patients with all year round hay-fever are given in table 6.

An analysis of the skin reactions obtained in these patients who had perennial hay-fever and who were sensitive to house dust extracts indi-

TABLE 6—Occurrence of Skin Reactions in Twenty Dust Sensitive Patients with Hay Fever

Food Proteins	Patients Giving Reactions		Inhalant Proteins	Patients Giving Reactions	
	Number of	Per Cent		Number of	Per Cent
Wheat	2	10	Dust	20	100
Corn	2	10	Leathers	13	65
Oats	1	5	Horse	6	30
Rice	1	5	Cat	4	20
Legs	2	10	Rabbit	1	5
Milk	1	5	Sheep	5	25
Fish	1	5	Silk	2	10
Nuts	2	10	Miscellaneous	7	35
Meats	1	5	Total animal	17	85
Fruits	4	20	Orris root	5	25
Vegetables	2	10	Tree pollen	0	0
Beverages	0	0	Spring pollen	14	70
Spices	1	5	Wall pollen	8	40
Total food	9	45	Total pollen	15	75

cates that sensitization to food and animal emanation proteins was about as frequent as in the series of dust sensitive patients with asthma. The frequency of pollen sensitization was greater than in the former series. This is probably due to the type of hay-fever occurring in California where there is pollen in the air throughout ten months of the year. However, I included in this series only patients who had all year round hay-fever, excluding the large number of purely seasonal pollen cases. In spite of this fact the multiplicity of types and number of sensitizations in patients who have perennial hay-fever and who are sensitive to house dust is demonstrated.

Single sensitization to orris root as a cause of perennial hay-fever is occasionally encountered. However, most patients who react to orris root also react to other proteins. The fact that food sensitization may also produce constant nasal congestion must be recognized.

An analysis of the reactions in this series shows that I could not be sure that dust sensitization alone was responsible for all the symp-

toms in any patient. Though the reactions to dust extracts in a few cases were stronger than those to other substances, each patient gave one or more slight or definite reactions to proteins other than those of dust. Thus certain patients with all year round hay-fever were pollen sensitive and other patients with symptoms indicating only pollen sensitization have been found to have persisting trouble throughout the year, and have given other reactions as well to dust proteins. Thus, to do justice to the hay-fever patient who has even slight symptoms throughout the year, routine testing with a large number of proteins of all type should be done.

#### TREATMENT

House dust sensitization can often be controlled by a thorough cleaning of the living rooms, and especially the bedroom, of the patient. In most cases, furnishings made from animal hair and wool should be eliminated. Such procedure is usually effective if other sensitizations such as food or pollen, are adequately controlled.

Those patients, however, who give marked reactions to house dusts may require desensitization to the active principles of several dusts in order to protect them. In certain cases it may be advisable to extract the dusts of several different rooms or of the upholstery or mattresses, in order to discover the actual source of dust sensitization indicated by history and skin testing. Treatment with such extract may then be advisable. The initial dose of a house dust extract should be 0.1 cc of the dilution that just fails to give a skin reaction. In some cases, it has been necessary to start with a solution diluted 10, 50, 100 or, as in two cases, 3,000 times. Spivacke reports two severe constitutional reactions after the injection of 0.1 cc of an undiluted extract. Such reactions must be prevented if possible.

#### VALUE OF TESTING AND TREATMENT WITH HOUSE DUST EXTRACTS

The main value of testing with dust extracts is in the indication of a type of sensitization active in the etiology of the patient's disease. Positive reactions to dust extracts should also make one suspicious of sensitization to other proteins, especially to animal emanation and pollen proteins, as demonstrated in the data in this article. Thus, the usual multiplicity of sensitizations in the patient with asthma or hay-fever must be kept in mind in the discussion of any one type such as I am considering here. House dust sensitization, however, is of great importance, and the positive dust reaction helps to demonstrate such sensitization to the physician and to emphasize the importance of the control of the house dust factor to the patient. I agree with Cooke and Meyer that such testing with dust extracts should be a matter of routine in all patients with asthma or perennial hay-fever.

The results obtained from the treatment with dust extracts are somewhat difficult to evaluate, since other types of sensitization were usually under control. However, my impression is that definite benefit was derived and that an attempt should be made to desensitize these patients with dust extracts to which they give strong reactions, especially if other skin reactions are small or indefinite.

#### CONCLUSIONS

1 It has been shown that 42 per cent of a series of 162 patients with asthma gave reactions to house dust extracts and that twenty patients with perennial hay-fever also gave such reactions.

2 Dust reactions have been obtained in all age groups with the scratch test.

3 A large number of patients have a characteristic history of dust sensitization.

4 The necessity of testing with a large number of stock and autogenous dust extracts is demonstrated.

5 Dust reactions may depend on one substance or on a summation of lesser reactions to several substances, such as animal emanations, orris root, pollens, and various fabric dusts, and that the possibility of an unknown specific substance in house dust is unlikely.

6 The data collected show that reactions to dust rarely occur without one or more other reactions to proteins commonly used in testing.

7 Desensitization to house dust extracts which give definite reactions in the patient is probably advisable in cases in which a marked history of dust sensitization is present.

# THE VALUE OF HISTAMINE AS A TEST FOR GASTRIC FUNCTION \*

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PHILADELPHIA

Histamine (B-imidazolethylamine) is derived from the amino-acid histidine, an almost universal constituent of proteins. It is evolved by decarboxylation in an appropriate medium by bacteria. Koessler and Hanke have shown that certain strains of *Bacillus coli* and other bacteria are capable of producing histamine from histidine in the presence of an available source of carbon such as glycerol or glucose, plus a source of nitrogen (potassium nitrate ammonium chloride or both) in the presence of oxygen. They believe that histamine is formed in the bowel by bacteria in order to neutralize an excessive acidity produced from glycerol. These observers have shown that histamine is a normal constituent of the cecum and feces of man in sufficient amounts to be dangerously toxic. The reason for the absence of toxicity is not established definitely. Hanke and Koessler<sup>1</sup> believe that histamine is rendered pharmacologically inert in its passage through the intestinal wall. It is an exceedingly active substance physiologically, and when injected subcutaneously or intravenously, causes marked fall in blood pressure, dilatation of the superficial blood vessels and marked increase in gastric secretion. If given in sufficient dosage, symptoms of shock will ensue.

The only action of histamine with which we are concerned at present is its effect on gastric secretion. The manner in which gastric secretion is stimulated by the amine is not settled. Rothlin and Grundlach<sup>2</sup> maintain that its action is caused by vagus stimulation. Koskowski and Popielski<sup>3</sup> believe that it acts directly on the gastric secretory cells. Gutkowski,<sup>4</sup> in seeking to explain the latent period of stimulation, demonstrated that when histamine is slowly injected into the blood, it produces gastric secretion. He further found a gastric response after

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1 Koessler, K K and Hanke, M T. J Biol Chem **39** 497 (Oct) 1919

2 Rothlin E and Grundlach R. The Influence of Histamine on Gastric Secretion Arch internat de physiol **17** 52, 1921-1922

3 Popielski, L. Histamine as a Strong Gastric Stimulant, Arch f d ges Physiol **178** 214 1920

4 Gutkowski, B. Stimulation of Gastric Juice of Slow Intravenous Injection of Histamine Compt rend Soc de biol **91** 1345 (Dec) 1924, Mechanism of the Action of Histamine in Promoting Gastric Secretion, Compt rend Soc de biol **91** 1349 (Dec) 1924

the subcutaneous injection of the drug into the posterior extremity of an animal whose only communication with the rest of the body was vascular. Ivy and Javots<sup>5</sup> have succeeded in producing histamine secretion in a "denervated" Heidenhain pouch, indicating that the mechanism of secretion is not nervous.

The effect of histamine on the human stomach was first observed by Carnot, Koskowski and Liebert<sup>6</sup> in 1922. On injecting from 0.75 to 1.75 mg. of the drug subcutaneously, they observed an increase in the flow of gastric juice in from thirty to fifty-five minutes, with an absolute increase in free and total acidity and in proteolytic activity. Matheson and Ammon<sup>7</sup> observed the effect of histamine on twelve convalescent patients. They used eiganine acid phosphate, which contains approximately one third of the base histamine. One and five-tenths milligrams of the salt was injected subcutaneously, and psychic stimulation was carefully avoided. They reported an increase in hydrochloric acid and in total acid starting in fifteen minutes, the maximum increase not being reached until from one-half to one hour after the injection. The maximum proteolytic activity as determined by the Mett method was reached earlier than the high acid level. They report a marked decrease in the amount of stomach mucus after injection of histamine in cases in which mucus was plentiful before the injection of this drug. This factor may influence the degree of acidity, according to these observers.

Lim, Matheson and Schlapp<sup>8</sup> corroborated the foregoing observations, they assert that histamine does not produce any direct effect on biliary or pancreatic secretion. They devised a method by which they prevented the entrance of gastric juice into the duodenum or duodenal secretions into the stomach. This observation was based on three cases. Gumpertz and Voorhaus<sup>9</sup> called attention to the value of histamine as an agent of differentiating true from pseudo-achylia. They injected 1 cc. of a 1:1,000 solution of the base subcutaneously and made extractions on the fasting stomach until the acid curve returned to normal. They report a marked response in normal persons as well as in persons with hypo-acidity. In a series of cases of supposed achylia gastrica, only 41 per cent turned out to be true achylia after injection of histamine. Dobson<sup>10</sup> observed the effect of histamine in seventeen

5 Ivy, A. C., and Javots, A. J. *Am J Physiol* **71** 604 (Feb.) 1926.

6 Carnot, P., Koskowski, W., and Liebert, E. Influence of Histamine on the Digestion Secretion in Man, *Compt rend Soc de biol* **86** 575, 1922.

7 Matheson, A. R., and Ammon, S. E. Effect of Histamine on Human Gastric Secretion, *Lancet* **1** 482 (March 10) 1923.

8 Lim, R. K. S., Matheson, A. R., and Schlapp, W. New Gastro-Duodenal Technic, *Edinburgh, M J* **30** 262 (July) 1923.

9 Gumpertz, L. M., and Voorhaus, M. G. Action of Histamine on Human Gastric Secretion, *J Lab & Clin Med* **11** 14 (Oct.) 1925.

10 Dobson, H. N. Effect of Histamine on Gastric Secretion, *J A M A* **84** 158 (Jan 17) 1925.

cases The observations were made on fasting stomachs, and the secretion was analyzed up to one hundred and fifty minutes He classifies his cases in three groups (1) those in which hydrochloric acid is intermittently present, as shown by fractional analysis, (2) those in which hydrochloric acid is absent, as shown by the fractional method, but in which there is a definite response to histamine, and (3) those in which hydrochloric acid is persistently absent, as shown by both methods Recently Carnot and Liebert<sup>11</sup> have advocated the superiority of the histamine test over the test meal for gaging gastric function The absence of food prevents the fixation of the acid and ferment by the ingested protein Their observations were made forty-five minutes after injection of 1 mg of histamine

We have been impressed with the difficulty in the diagnosis of achylia and interested in the mechanism of its production The fractional gastric analysis as outlined by Rehfuess has been a routine procedure in our clinic for years Even following this method of analyzing gastric function, we have been confronted with a great many borderline cases of achylia In some instances a complete absence of mineral acid and enzyme was encountered, in others a transient trace of enzyme only was present and in still others an occasional trace of acid and enzyme occurred at one time, only to be absent at other times

In this report an effort has been made to study the effect of injection of histamine on the gastric secretion when given simultaneously with the meal of bread and water A comparison has been made between the gastric secretory response following the ordinary fractional analysis and the response after injection of histamine plus the test meal In both instances extractions were made every fifteen minutes for two hours or until the stomach was empty So far the reports on histamine are all based on an examination of the fasting stomach or one made after a water meal In this study 1 mg (1 cc of 1:1,000 solution) of histamine (Hoffman, LaRoche) was injected subcutaneously after the insertion of the tube and the evacuation of the residuum simultaneously with the ingestion of the meal

#### ACHLORHYDRIA

Twenty-one patients with so-called achlorhydria were examined in this manner, and the comparative secretory response can be seen in table 1 These cases were classified as achlorhydria following the fractional gastric analysis because of the absence of mineral acid throughout the two hour phase of gastric digestion Ten patients were studied two or more times by the fractional method without the use of

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11 Carnot, P, and Liebert, E Test Meals and Histamine Test for Determination of Secretory Activity of Stomach, *Medecine* 6:657 (July) 1925

TABLE 1—*Achlorhydria Tested by Ordinary Fractional Gastric Analysis, Gastric Analysis Following Injection of Histamine and Erection of Neutral Red*

No	Fractional Gastric Analysis										Histamine			Neutral Red		Remarks	Group
	Hydrochloric Acid	Acid	Enzyme	Hydrochloric Acid	Acid	Enzyme	Hydrochloric Acid	Acid	Enzyme	Acid	Enzyme	Venous	Muc				
111	0	50	20	40			40	65								Groups 2 and 3 with ordinary gastric ferment	3
112	0	30					25	40								Groups 1 or 2 with ordinary gastric ferment	3
113	0	10	0	10	0	0	0	5	0							Alcoholic	1
114	0	10	+			+	0	25	+			+	0			Group 2 with ordinary gastric ferment	2
116	0	10	0	10	0	0	0	20	0			0	0				1
117	0	15	0	10	0	0	0	35	0			0	0				1
118	0	15	0				0	15	0			0					1
121	0	20	0	15	0	0	0		0								1
124	0	25	15	30	+		20	35	+							Groups 2 and 3 with ordinary gastric ferment	3
125	0	20	0				0	20	+				0			No acid, remnant with histamine	3
126	0	5	0	15			0	32	+			+	±			Groups 1 and 2 with ordinary gastric ferment	3
127	0	20	8	27	+		25	30	+			+	+			Groups 2 and 3 with ordinary gastric ferment	3
131	0	20					0	15	0			0	0			Cancerous stomach	1
132	0	20	0				5	25	+			+				Group 1 to ordinary	3
133	0	10	0				0	10	0			0				Combined lateral sclerosis	1
134	0	30	0				0	15	0			+				Permeious anemia	1
135	0	20	0				0	15	0							Cancer	1
136	0	15	+				15	35	+							Group 2 with ordinary gastric ferment	3
137	0	15	0				0	10	0								
138	0	15	0				0	15	0			0				Bowel toxemia	1
141	0	5	0	10	0	0	5	20	+			+				Visceral syphilis, group 1 with ordinary gastric ferment	3

Diagnosis Achylia, group 1, achlorhydria, group 2, hypochlorhydria, group 3, twenty one cases

histamine In thirteen, the stomach's ability to excrete neutral red, after it had been injected either intravenously or intramuscularly, was tested The figures recorded in the table under hydrochloric acid and acid represent the highest level of free acid and total acid during the test The enzyme determination used was the simple milk test for rennet, a fifteen minute incubation period being followed In the last column a final classification of cases has been made, based on all three examinations, that is, ordinary fractional analysis, fractional histamine analysis and neutral red test

Group 1 True achylia gastrica, no hydrochloric acid or enzyme being present after ordinary fractional or histamine analysis, and absence of neutral red excretion by the stomach following its intravenous injection

Group 2 Achlorhydria, no mineral acid after ordinary or histamine analysis, but a trace of enzyme following the ordinary or histamine test or both

Group 3 Hypochlorhydria, reduced amounts of mineral acid and enzyme being present after injection of histamine

Of the twenty-one patients in whom hydrochloric acid was absent on initial examination, five gave positive tests for gastric ferment (cases 114, 124, 126, 127 and 136) In case 126, free acid and ferment were absent during two fractional tests, but a faint trace of rennet was present in the third analysis Almost invariably the enzyme in these cases was present only toward the end of the examination, from one and one-half to two hours after the meal The literature contains innumerable cases classified as achylia, based on a single extraction made anywhere from one-half to one and one-half hours after a test meal

Two of the five patients mentioned in the foregoing (cases 124 to 127) had hydrochloric acid on second analysis by the ordinary method This is not surprising, since the figures for total acid were unusually high at the time of the first examination These two cases were dropped from the achlorhydria group 2 to group 3 before the histamine test was used A high total acidity was also obtained in case 3 during the first analysis The second ordinary test revealed an acidity of 20 The injection of histamine into these three patients (cases 111, 124 and 127) caused a greater secretion of free and total acid, but they were dropped to group 3 before histamine was used The fractional gastric analysis on two occasions in case 114 showed an absence of hydrochloric acid but a trace of enzyme The injection of histamine did not cause any further response (no free acid was obtained) The neutral red test is of interest in this case Injection of dye into the muscle did not cause any gastric excretion After the intravenous injection of the dye, a trace appeared in the stomach Although this case cannot be classified

as one of true achylia, because of the presence of rennet, histamine did not cause an acid response. This case remains in group 2. We think it possible that this patient had potential achylia. In cases 126 and 136 there was free acid in the stomach after injection of histamine, but none after the ordinary test. Injection of histamine dropped these cases from group 2 to group 3. The six cases under discussion do not belong to the true achylia group 1.

There remain fifteen cases which, after one or several fractional Rehfuß tests, did not show any hydrochloric acid or rennet. Of this series which was potentially classified as belonging to group 1, four patients (cases 112, 125, 132 and 141) gave a gastric response to histamine. In case 125 there was enzyme after the injection of histamine but no free acid. It was placed in group 2. Both hydrochloric acid and enzyme appeared after histamine was used in the remaining three cases. They were lowered in the classification to group 3. The intravenous neutral red test was performed in cases 132 and 141. The dye appeared in the stomach, confirming the histamine test. Five patients (cases 112, 126, 132, 136 and 141) showed hydrochloric acid response to histamine when no acid was obtainable by the ordinary fractional method. In one patient (case 125), rennet was present after injection of histamine when both mineral acid and enzyme were absent after the Rehfuß test. Starting out with twenty-one cases which could have been classified as achylia gastrica by the fractional gastric analysis as ordinarily performed (without enzyme determination), only eleven remain in that group, following injections of neutral red, histamine or both. Undoubtedly, if one hour extractions had been practiced instead of the fractional method over a similar period, a greater number of cases in which achylia was suspected would have been encountered. In a large number of our cases of hypochlorhydria there was neither acid nor enzyme one hour after the test meal was given. Table 1 demonstrates clearly the value of repeated fractional studies, as the original diagnosis of achlorhydria was discarded in six cases after a second or third test was made even before histamine was used.

Only eleven cases (53 per cent) withstood the critical studies to eliminate achylia gastrica. Injection of histamine did not produce any gastric response. Seven of the patients also received injections of neutral red, the dye not being excreted by the stomach. The neutral red determinations confirmed the histamine test in each case in which both were performed with one exception (case 125). The dye was injected intramuscularly in this instance. It was not excreted by the stomach suggesting achylia, although enzymes were present after the ordinary and the histamine fractional test. This confirms our previous observation that the muscular injection of neutral red in the prescribed dosage

is insufficient to cause it to appear in some stomachs even in the presence of slight secretory function <sup>12</sup>

HYPOCHLORHYDRIA

A similar comparison between the Rehfuß test and the histamine injection simultaneously with the test meal was made in twenty-nine cases of hypo-acidity. The degree of free and total acidity throughout both tests is compared in table 2. The composite free and total acid curves of these cases have been drawn, with and without the use of histamine (chart 1). It will be noted that hypochlorhydric cases as a group

TABLE 2—Comparison Between Average Acidity, for Each Fifteen Minute Extraction, with Ordinary and Histamine Fractional Gastric Analysis

Minutes after Meal	Hydrochloric Acid Ordinary Gastric	Hydrochloric Acid Histamine Gastric	Total Acid Ordinary Gastric	Total Acid Histamine Gastric
Hypochlorhydria Group				
15	2.6	6.2	12.5	17.0
30	2.6	12.4	15.6	25.3
45	3.1	18.6	19.2	32.5
60	7.7	22.3	24.7	36.3
75	7.7	23.7	23.2	37.5
90	10.2	24.8	25.9	37.9
105	9.4	22.9	25.4	35.6
120	13.1	17.4	28.4	31.9
Normacid Group				
15	7.3	16.0	21.5	27.7
30	11.1	26.8	25.6	42.3
45	21.3	34.5	38.2	49.5
60	30.9	40.5	49.6	60.4
75	31.2	40.6	51.5	60.0
90	30.0	37.0	50.0	53.5
105	24.0	40.0	49.4	55.7
120	34.0	35.0	51.0	52.5
Hypochlorhydria Group				
15	16.1	17.8	33.8	35.7
30	37.5	30.0	54.4	46.4
45	52.5	45.0	74.4	61.2
60	54.4	55.0	75.0	70.7
75	58.1	51.4	83.1	68.6
90	55.6	49.3	72.5	67.1
105	46.7	59.0	64.2	79.0
120	42.0	52.0	58.0	73.0

have a much higher secretory response after the use of histamine than after the Ewald meal alone. The higher secretion level for free and total acid starts before the fifteen minute extraction and persists for two hours. The highest level of histamine response is obtained from forty-five to one hundred and five minutes after the injection in this group. In twenty-two cases a comparison has been made between the appearance time and the duration of acid secretion by the ordinary fractional and histamine fractional methods (table 3). The average appearance time of hydrochloric acid after the ingestion of the Ewald meal was forty-eight minutes. When histamine was injected with the meal, the

12 Piersol, George Morris, Bockus, H. L., and Bank, J. The Practical Value of Neutral Red as a Test for Gastric Secretory Function, *Am J M Sc* 170:405 (Sept.) 1925

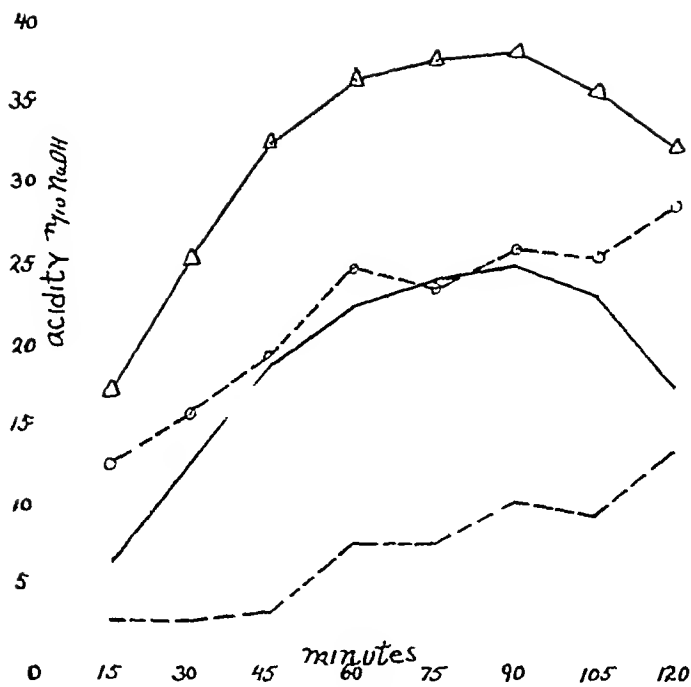


Chart 1—Hypochlorhydria after injection of histamine In these charts the broken line indicates the free acid curve when histamine has not been injected, the dash and circle line, the total acidity, the solid line indicates the free acidity after the injection of histamine, the solid and triangle line, the total acidity

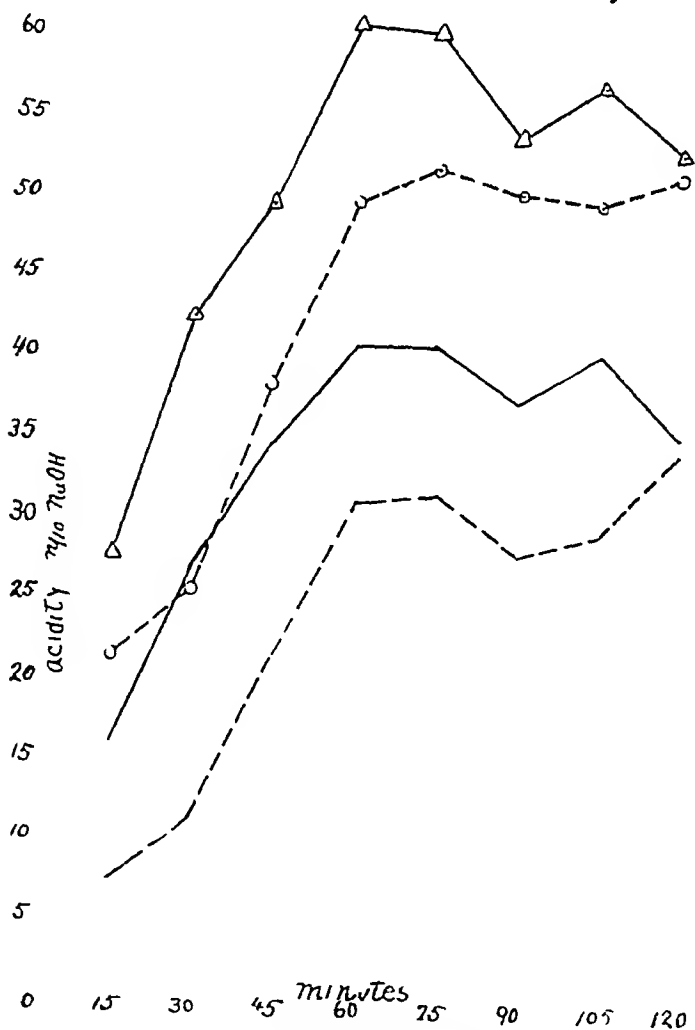


Chart 2—Normal acidity

average appearance time was shortened to thirty minutes. The average duration of the secretion curve following the meal alone was fifty minutes in this group as compared with seventy-eight minutes when histamine was injected simultaneously with the meal. Histamine in cases of reduced acidity causes the acid secretion to appear earlier and persist over a longer period.

In seven cases of hypochlorhydria which were achlorhydric to ordinary fractional test, injection of histamine caused free acid to make an average appearance in forty minutes and to persist for forty-one minutes. When these cases are compared with those included in table 3 which

TABLE 3—*Hypochlorhydria: Comparison Between the Appearance Time and Duration of Acid Secretion During Fractional Gastric Analysis with and without Histamine*

Case	Ordinary Gastric		Fractional with Histamine	
	Appearance Time in Minutes	Duration of Secretion in Minutes	Appearance Time in Minutes	Duration of Secretion in Minutes
111	30	30-90	45	45-120
124	75	75-105	45	45-90
127	45	45-60	45	45-120
122	45	45-90	45	45-120
123	15	15-120	15	15-90
128	75	75-90	30	30-120
129	75	75-120	75	75-120
130	90	90-120	15	15-120
131	105	105-120	30	30-120
132	60	60-105	60	60-120
133	75	75-90	30	30-120
134	15	15-105	15	15-105
135	60	60-90	30	30-120
138	30	30-60	15	15-105
140	15	15-45	15	15-90
141	15	15-120	15	15-120
142	15	15-60	15	15-75
143	15	15-120	15	15-105
144	45	45-120	15	15-60
145	60	60-105	15	15-120
146	30	30-75	15	15-120
147	60	60-120	60	60-120
Group average	48	50	30	78

were hypochlorhydric after ordinary fractional a definite trend downward in secretion is noticed. The acid appears later and persists for a shorter period in the former group (group 2 with ordinary fraction). Here is further confirmatory evidence of the gradual gradation between normacid and achylia stomachs.

#### NORMAL ACIDITY

Eleven cases approximating normal gastric acidity were compared in a similar manner (table 2). Most of these cases were possibly below normal in acidity but were considered too high to be included in the hypochlorhydria group. A composite curve of acidity in this group (chart 2) reveals an increase in degree of secretion when histamine was injected at the time of ingestion of the meal. The appearance time of secretion was earlier and the duration of secretion longer when histamine

was used. However, the secretory response to histamine was not nearly so great as in the hypochlorhydria group. It would appear that as the stomach secretion approximates normal, it responds less and less to histamine. Possibly it cannot secrete an acid greater than its high normal level.

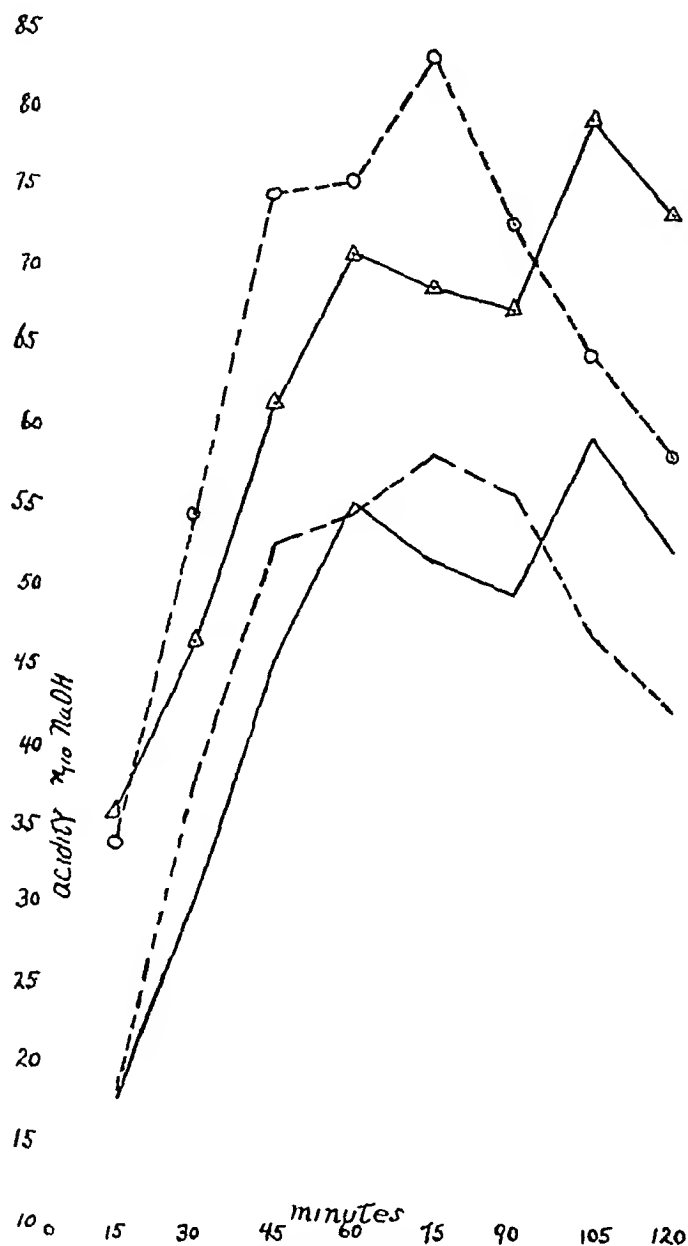


Chart 3—Hyperchlorhydria

#### HYPERCHLORHYDRIA

Injections of histamine were given to eight patients who were classified in the hyperacid group after ordinary gastric analysis. None of them had gastric stasis. No definite gastric pathologic change was diagnosed in any case. It will be seen by consulting the composite curve (chart 3) that the secretion was not increased after the use of histamine.

In fact, the free and total acid line with histamine is below the line of the ordinary fractional except at one hundred and five and one hundred and twenty minutes after the meal. This seems to be in accordance with Carlson's contention that the stomach cannot secrete an acid of more than normal concentration.

#### CONSTITUTIONAL EFFECT

We have not had any alarming reactions following the injection of 1 mg. of histamine. Almost invariably, the exposed parts of the body became red within a few minutes after the injection, and the blood pressure dropped on an average of 10 mm. of mercury. Occasionally a patient complained of headache. There was slight acceleration of the pulse rate. Only one patient, who had pernicious anemia, had a more severe reaction, and it was not alarming. She complained of extreme weakness and depression which lasted for several hours. An interesting observation was made of the physiologic action of histamine on another patient. The injection of histamine was given when he was under the influence of atropine mydriasis. Several minutes after the injection was given, his vision suddenly returned to normal.

#### SUMMARY

A comparison has been made between the ordinary fractional gastric analysis and a fractional analysis of the stomach following injection of histamine which was given simultaneously with the ingestion of the meal. This is the first time the effect of histamine on the stomach during the digestive phase with a carbohydrate meal has been studied. Space does not permit a discussion of a clinical or etiologic consideration of achylia gastrica. We consider achylia a rare entity, although hypochlorhydria and achlorhydria are encountered rather frequently.

1. Only 53 per cent of the stomachs in which achlorhydria was diagnosed after the Rehfuess test failed to secrete gastric juice after injection of histamine. However, in six of the twenty-one cases the diagnosis of achylia was discarded by repeated fractional tests.

2. The great bulk of literature on achylia gastrica is worthless. It is likely that only a small proportion of such cases which were reported previous to the last few years were really cases of achylia gastrica.

3. We believe that the diagnosis of achylia gastrica is impossible when the single extraction method is used.

4. Ordinary fractional gastric analysis, including enzyme determinations as well as acid titration, if frequently repeated, probably will be a safe method of diagnosing achylia in most cases. However, there will remain a few cases in which acid or enzyme will not be found by this method, but in which there will be a secretory response to histamine.

5 In the present state of our knowledge of achylia, the diagnosis had better not be made definitely without confirmation by the histamine test

6 The failure of the stomach to excrete neutral red after its intravenous injection has proved equally reliable in the diagnosis of achylia in our hands

7 In cases of hypochlorhydria injection of histamine caused a definite increase in the acidity throughout the period of gastric digestion of the Ewald meal. It caused mineral acid to appear earlier and prolonged the period of secretion

8 In cases of normal acidity, injection of histamine caused an elevation of the degree of acidity, but to a lesser extent than in cases of reduced gastric acidity

9 In cases of hyperacidity, the stomach did not respond to the subcutaneous injection of histamine

10 Histamine proved safe in our hands, and we believe it is of distinct value in the differentiation between achylia and achlorhydria or hypochlorhydria

11 We do not believe that injection of histamine with or without a water meal is in any way comparable to the fractional gastric analysis as a general test for gastric function. We believe with Rehfuess that the fractional method yields information as to gastric work, and that a definite load must be imposed on the stomach in order to judge its ability to perform its function. The normal physiologic load is food, and that substance must be used in order to get the maximum information concerning the secretory and motor function. We feel that the performance of the ordinary fractional gastric analysis and the histamine gastric analysis as described will yield more information than either alone in stomachs with a low acidity and that both tests should be made in such cases

# THE COURSE OF HYPERTHYROIDISM UNDER IODINE MEDICATION \*

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When the iodine remission in hyperthyroidism is complete, it is one of the most striking of therapeutic transformations. The process is now well known.<sup>1</sup> During an investigation of this remission in 1923,<sup>2</sup> two other associated reactions of hyperthyroidism to iodine were noted, namely, the gradual return of the disease during continued iodine administration, when there was no operative intervention, and the sudden exacerbation after the iodine was stopped. Repeated clinical experiences with these three phenomena have led to the impression that they form a sequence through which the disease will pass when the patient is treated with daily doses of iodine for a definite period. This whole course cannot be experimentally studied in patients, since it must be interrupted by thyroidectomy, but the regularity with which recurrence and postiodine reaction occur when the opportunity arises leaves little doubt that they are constant phases of the effect of iodine on the course of hyperthyroidism. The material covering these undesirable phases is necessarily limited to clinical mistakes, especially to those instances in which the actual course can be demonstrated by determinations of the metabolic rate.

Only one small part of this process, the iodine remission which occurs during the first few days, is of any practical value. The remaining weeks under iodine medication and several weeks after the iodine is stopped are occupied by the reestablishment of the disease. Hence, unless the remission is to be used as a period for operation, the administration of iodine to patients with hyperthyroidism is without final benefit, and usually harmful. Many of the patients coming to this clinic have been given iodine for a long time, and thus the opportunity for the best preoperative preparation by the primary iodine remission

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\* From the Medical Department of Northwestern University Medical School. Cases studied are from the services of Dr. Charles A. Elliott, Dr. Allen B. Kanavel and Dr. Harry M. Richter at the Wesley Memorial Hospital.

1 Plummer, H. S. Results of Administering Iodine to Patients Having Exophthalmic Goiter, *abstr. J. A. M. A.* **80** 1955 (June 30) 1923. Plummer, H. S., and Boothby, W. M. Value of Iodine in Exophthalmic Goiter, *J. Iowa M. Soc.* **14** 66 (Feb.) 1924. Starr, P., Segall, H. N., and Means, J. H. Effect of Iodine in Exophthalmic Goiter, *Arch. Int. Med.* **34** 355 (Sept.) 1924. Cowell, S. J., and Mellanby, E. Effect of Iodine on Hyperthyroidism in Man, *Quart. J. Med.* **18** 1 (Oct.) 1924. Fraser, F. R. Iodine in Exophthalmic Goiter, *Brit. M. J.* **1** 1 (Jan. 3) 1925.

2 Starr, P., Segall, H. N., and Means, J. H. Effect of Iodine in Exophthalmic Goiter, *Arch. Int. Med.* **34** 355 (Sept.) 1924.

has been lost. If the physician wishes to cooperate with the surgeon in the treatment of patients with this condition, he should not administer iodine as a cure. It cannot benefit his patient permanently.

#### THE COMPLETE IODINE EFFECT

The typical complete course (as represented by the basal metabolic rate) in all types of hyperthyroidism, when the patient is treated with daily large doses of iodine in any form, is illustrated in chart 1. The process consists of three stages. First, there is a remission of the disease, this has been found by many observers.<sup>1</sup> Second, there is a recurrence under continued iodine therapy.<sup>3</sup> Third, there is a postiodine reaction consisting of a self-limited period of increased metabolism, after which the rate returns to the level established before iodine was given.<sup>2</sup>

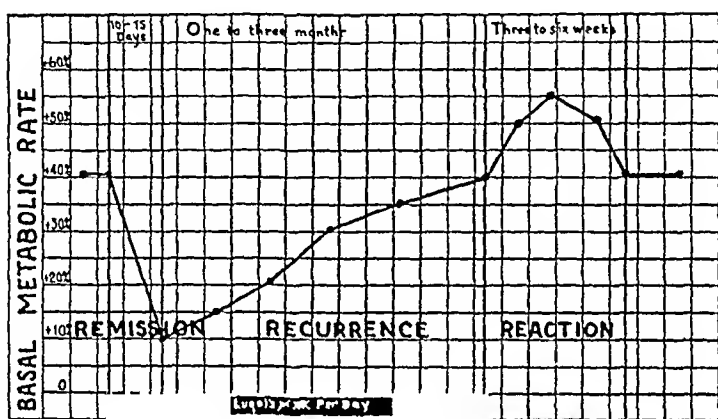


Chart 1—The metabolic rate in hyperthyroidism under administration of iodine and after it is discontinued. It is assumed that the metabolic rate before iodine is about +40 per cent, the remission then occurs rapidly, and as here represented, is complete, the recurrence is more gradual, and after the iodine is stopped, there is a sharp self-limited period of increased metabolic rate, the postiodine reaction. The time periods given are only approximate.

Chart 1 illustrates the iodine action when fully effective. There is, however, every gradation of this effectiveness, from those cases in which the metabolic rate is entirely unchanged by the usual dosage of iodine, to those in which the disease seems to stop suddenly when iodine is administered. Occasionally, the recurrence seems long and gradual, only to be followed by the postiodine reaction when the iodine is discontinued. The postiodine reaction may be characterized by a degree of hyperthyroidism not present before the iodine was given. It occurs following remission and also after recurrence.

<sup>3</sup> Starr, P. Segall, H. N. and Means, J. H. Effect of Iodine in Exophthalmic Goiter, *Arch. Int. Med.* **34** 355 (Sept.) 1924. Cowell, S. J. and Mellanby, E. Effect of Iodine on Hyperthyroidism in Man. *Quart. J. Med.* **18** 1 (Oct.) 1924. Fraser, F. R. Iodine in Exophthalmic Goiter, *Brit. M. J.* **1** 1 (Jan. 3) 1925.

## THE IODINE REMISSION

In a previous paper,<sup>2</sup> the frequency of occurrence of the iodine remission in a series of patients with hyperthyroidism was given as 80 per cent. Plummei<sup>4</sup> had reported a similar and even greater frequency, but it must be emphasized that there will be great variation in the extent of remission. An analysis of thirty-six cases in which the patients were recently observed is presented in table 1. This group is unselected and includes patients with every type of hyperthyroidism, of widely different ages and with many varieties of pathologic changes in the thyroid gland. In eight (first two groups) or about one fourth of the thirty-six, there was little or no remission, while in twenty-eight (the remaining groups) or about three fourths, there was a reduction in the metabolic rate of 50 per cent or more. In cases showing little

TABLE 1—*Frequency and Degree of Iodine Remission. Analysis of Data of Thirty-Six Unselected Clinic Patients Exhibiting All Types of Hyperthyroidism*

Reduction of Metabolic Rate to Normal, Percentage	Number of Patients	Average of All First Metabolic Rates, Percentage	Average Period Under Iodine, Days	Average Dose of Lugol's Solution Daily, Minims	Average of All Last Metabolic Rates, Percentage
0	4	+53	12	45	+53
25	4	+51	7	30	+37
50	15	+67	12	30	+36
75	9	+55	11	45	+20
100	4	+60	15	30	+8

reduction of metabolic rate there is often a gain in weight and a slowing of pulse, with general clinical improvement indicating that there is a true remission, although of slight grade, in progress. Including such cases, the frequency of remission is probably over 90 per cent. Since only thirteen, or about one-third of this group, have a remission approaching normal, the postponement of operation in the hope of complete reduction of metabolic rate must not be delayed after the average period usually necessary for induction of the iodine remission. This period has been shown to be from ten to fifteen days. Recurrence begins gradually after this. The total period of low metabolic rate varies from a few days to three weeks. The actual reversal of the remission probably begins immediately after it is complete.

## IODINE REMISSION IN NONEXOPHTHALMIC HYPERTHYROIDISM

It has previously been shown that the iodine remission occurs in cases of hyperthyroidism clinically described as exophthalmic goiter.<sup>2</sup> From an analysis of recent clinical material, it is evident that cases of

4 Plummer, H. S., and Boothby, W. M. Value of Iodine in Exophthalmic Goiter, J. Iowa M. Soc. 14: 66 (Feb.) 1924.

hyperthyroidism of the chronic type, which are not exophthalmic goiter, are also subject to the iodine remission. This conclusion comes as a result of using Lugol's solution in preoperative preparation in every variety of hyperthyroidism, and it is evident that any distinction concerning the primary iodine effect is not to be made between exophthalmic goiter, toxic goiter, or adenomatous goiter with hyperthyroidism.

In table 2 the remissions in twenty patients with toxic goiter and adenomatous goiter with hyperthyroidism are classified on the same basis as in table 1. It is to be noted that five, or one-fourth, had a remission of 25 per cent or less, while fifteen, or three-fourths, had a remission of 50 per cent or more. Thus, the frequency and extent of remissions in this group is the same as for the unselected group and practically the same as for the series of patients with exophthalmic goiter which was reported previously.<sup>2</sup>

TABLE 2—Remissions in Twenty Patients with Toxic Goiter, Including Adenomatous Goiter with Hyperthyroidism

Extent of Reduction of Metabolic Rate, Percentage	Number of Cases
0	2
25	3
50	7
75	7
100	1

A typical 75 per cent remission occurred in the following case:

Mrs. C. M., aged 46, had had slight enlargement of the thyroid body for several years, there was a palpable nodule in the left lobe. Following an infection of the leg two years before entrance, she complained of weakness, dyspnea and palpitation. On examination, exophthalmos was not found, and auricular fibrillation was present. The basal metabolic rate was +38 per cent. After fourteen days, during which 20 minims of Lugol's solution was given each day, the rate was +16 per cent, practically a complete remission. Pathologic report after thyroidectomy was differentiated fetal adenoma of the thyroid.

The other cases classified in table 2 are entirely analogous to this. The average age of the patients was 46 years, exophthalmos was not present, cardiac symptoms were predominant, there were five patients with auricular fibrillation, pathologic reports are uniformly of adenomas or adenomatous growth.

In chart 2 are presented the metabolic rate curves of seven patients whose clinical history and physical and pathologic examination showed an adenomatous goiter with hyperthyroidism. The primary iodine remission occurred in all of these patients. The average decrease of metabolic rate under iodine was thirty points. As a result of this experience, the statement that the primary iodine remission occurs and may be complete in all types of hyperthyroidism seems justified.

## ABSENCE OF IODINE REMISSION

The converse of this is the fact that iodine as used in this work, that is, in doses of from 15 to 45 minims of Lugol's solution a day, has occasionally failed to produce remission in every clinical type of hyperthyroidism. The data of a group of five patients with exophthalmos and hyperplastic thyroids have been published previously.<sup>2</sup> Although clinically and pathologically representative of exophthalmic goiter, they did not have the primary iodine remission. In a more recent study, the metabolic rate curves and the characteristics of patients with all types of hyperthyroidism who had only a 25 per cent remission or less, are shown in chart 3. The ages range from 38 to 65 years, the goiter was imperceptible in two, and had been present from three months to thirty years in the others, the symptoms had been present an equally variable length of time, exophthalmos was absent

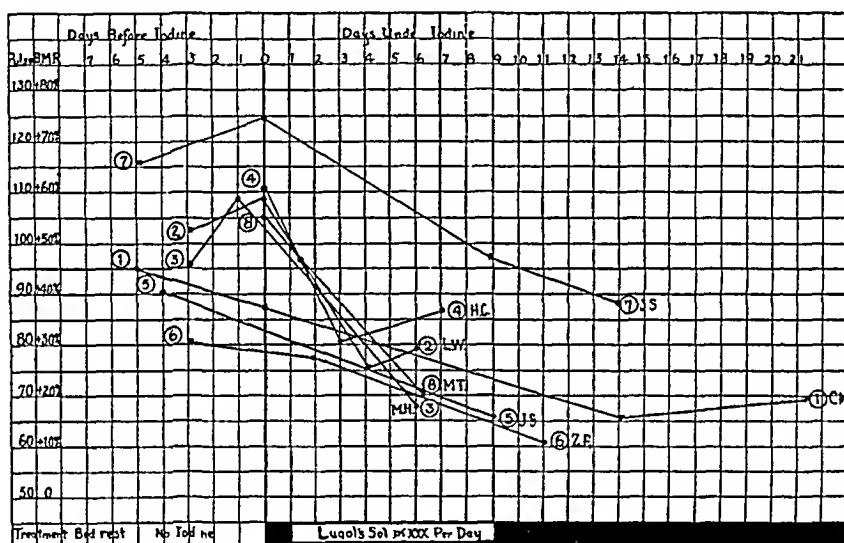


Chart 2—Effect of iodine on metabolic rate in adenomatous goiter with hyperthyroidism. Eight patients showed iodine remission. 1, aged 46, duration of goiter not known definitely, duration of symptoms two years, exophthalmos not present, pathologic report, fetal adenoma, 2, aged 46, duration of goiter ten years, duration of symptoms twenty years, exophthalmos not present, pathologic report adenoma of thyroid, 3, aged 55, duration of goiter five years, duration of symptoms five years, exophthalmos not present, pathologic report adenoma of thyroid, 4, aged 52, duration of goiter more than two years, duration of symptoms five years, exophthalmos not present, pathologic report multiple adenomas, 5, aged 52, duration of goiter thirty-five years, duration of symptoms five years, exophthalmos not present, pathologic report fetal adenomas, 6, aged 62, duration of goiter more than four years, duration of symptoms seven years, exophthalmos not present, pathologic report degenerating adenomas, 7, aged 62, duration of goiter three years, duration of symptoms three years, exophthalmos not present, pathologic report colloid goiter, adenomatous growth, 8, aged 52, duration of goiter not known definitely, duration of symptoms two years, exophthalmos not present, pathologic report colloid adenoma. Operation followed the last determination in all cases.

in three, and marked in one, the pathologic change ranges from marked acute hyperplasia to multiple adenomas. There would seem, so far as these observations are concerned, to be no clinical or pathologic features characteristic of these processes which are resistant to iodine medication as compared with those which yield to this therapy.

To summarize the data relative to the iodine remission: (a) A more than 50 per cent reduction of basal metabolic rate may be expected in at least three fourths of all patients with all types of hyperthyroidism, including adenomatous goiter with hyperthyroidism, within fifteen days, when from 15 to 45 (0.9 to 2.8 cc) minims a day of Lugol's solution is first given, (b) in about one fourth or less of all patients with whatever type of hyperthyroidism, there will be less than a 25 per cent reduction of metabolic rate, (c) no clinical or pathologic characteristic distinguishes these processes resistant to iodine as it is now used, from those which yield to iodine.

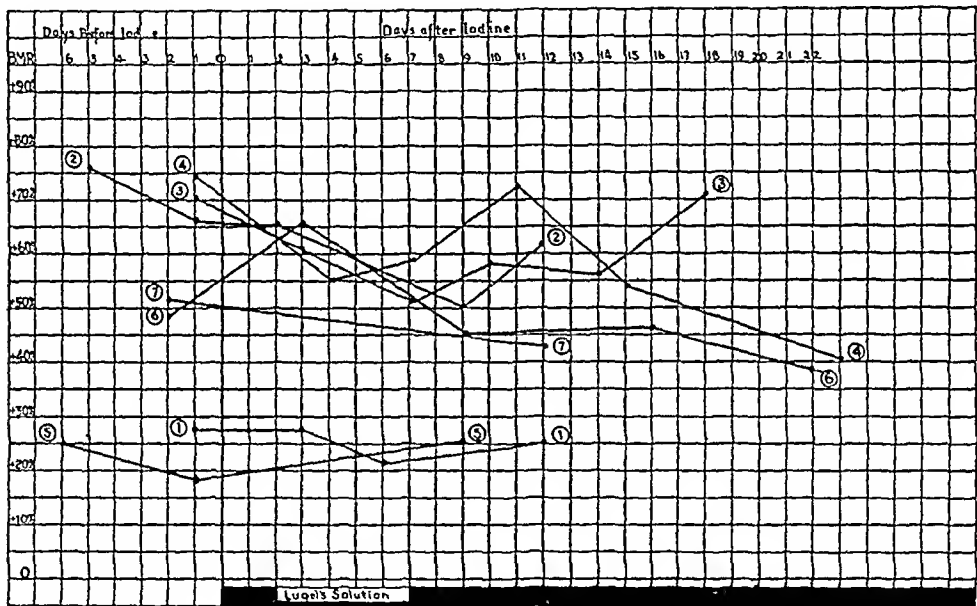


Chart 3—Examples of absence of iodine remission. Metabolic rate curves: 1, aged 59, duration of goiter not known definitely (small), duration of symptoms seven years, exophthalmos not present, pathologic report slightly adenomatous growth on colloid thyroid; 2, aged 65, duration of goiter thirty-two years, duration of symptoms twenty years, exophthalmos not present, pathologic report colloid adenoma of thyroid; 3, aged 41, duration of goiter three months, duration of symptoms three months, exophthalmos  $\pm$ , pathologic report hyperplastic thyroid, moderate, marked; 4, aged 47, duration of goiter two years, duration of symptoms two years, exophthalmos  $++$ , pathologic report diffuse adenomatous colloid goiter; 5, aged 39, duration of goiter ten years, duration of symptoms two years, exophthalmos not present, pathologic report multiple colloid adenomas; 6, aged 40, duration of goiter not known definitely (small), duration of symptoms nine years, exophthalmos  $+++$ , pathologic report acute hyperplasia marked; 7, aged 38, duration of goiter nine months, duration of symptoms nine months, exophthalmos  $+$ , pathologic report moderate and marked hyperplasia. Lugol's solution 10 minims (0.6 cc) three times a day began on zero line.

## RECURRENCE UNDER IODINE MEDICATION

The demonstration that after the iodine remission, even though iodine is continued, there will be a more or less gradual and immediate return of hyperthyroidism rests on experimental results and clinical experience. In the fall of 1923, a group of five patients at the Massachusetts General Hospital, who had had good remissions with iodine, was again given this medication in order to determine the possibility of continuous iodine control (chart 4). At the end of the second or third month, in all of these patients the metabolic rate was equal to the rate before iodine was given. A subtotal thyroidectomy was ultimately successful in all of them, so that the postiodine reaction could not be demonstrated. Four months had been wasted in an unsuccessful attempt to control the disease by iodine. Such detailed and measured proof

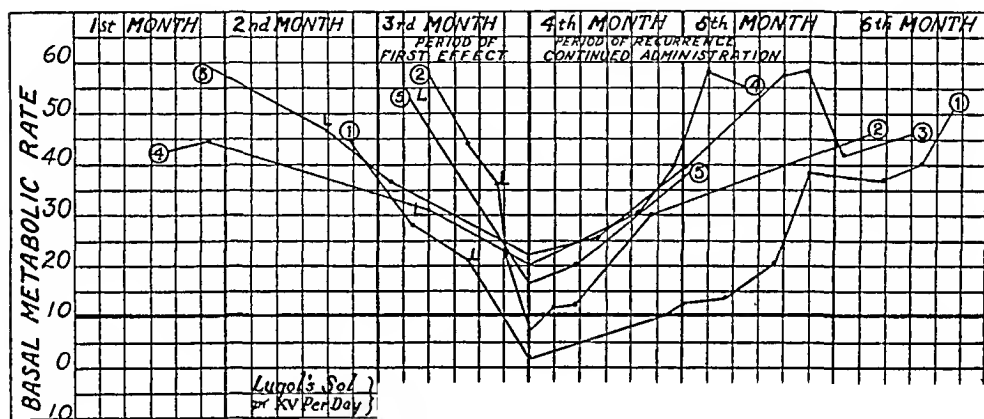


Chart 4—Remission and recurrence under iodine

that recurrence always follows remission is not abundant. In clinics in which iodine is used intelligently, operation interrupts hyperthyroidism before recurrence takes place. Occasionally, however, owing to a misconception of the course under iodine, such a demonstration occurs.

A recent case may be added to these. The metabolic rate of Mr. L. K. fell from +75 per cent to +11 per cent in fifteen days under the administration of Lugol's solution. It was thought that the disease must have been abated permanently. The patient was discharged with orders to continue the same dosage. During the next six weeks, although he gained weight, the basal pulse rate rose from 65 to 100, and the metabolic rate readings were successively +19 per cent, +35 per cent, and +47 per cent. It was evident that the disease had recurred in spite of the continuation of iodine therapy, and without further delay subtotal thyroidectomy was performed.

Additional evidence in favor of recurrence during treatment with iodine is found in a study of the previous medication given to patients with hyperthyroidism who finally came to the hospital for thyroidectomy. Of a recent series of seventy-five patients who were subjected to the

maximal thyroidectomy, twenty-five had received iodine for from three weeks to nine months before entrance. Some of these are instances of induced iodine hyperthyroidism, most of the patients had the disease before the iodine was given. It is chiefly because of these patients, in whom the opportunity for the primary iodine remission had been passed because of the mistaken practice of their physicians or themselves, that this report is published. A typical example may be cited.

Mrs V der W, aged 34, felt the onset of her second attack of hyperthyroidism six months before seeking medical attention. The metabolic rate on January 15 was +63 per cent, on March 25 it was +71 per cent, administration of Lugol's solution was started on March 27, on April 10 the rate was +15 per cent, and on April 20 it was +13 per cent. Although this was the optimal time for operation, it was decided to have the patient come to Chicago, and the operation was postponed, although she continued to take

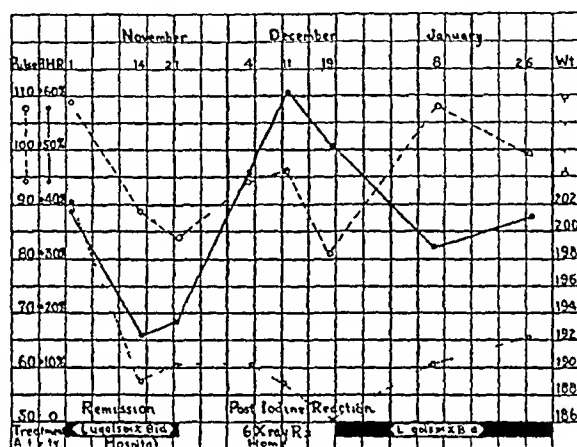


Chart 5—Postiodine reaction occurring immediately after remission. Mrs. C. M., chronic hyperthyroidism, pathologic report: adenoma of thyroid.

iodine until May 20. On May 29, the rate was +52 per cent. The opportunity for operation during the iodine remission, which in this case was nearly complete, had been lost.

To summarize: (a) Iodine cannot, as it is now given, control hyperthyroidism indefinitely. It should be used only for its primary effect, that is, as a preparation for operation. Recurrence follows remission, usually beginning within three weeks after the first administration of iodine.

#### POSTIODINE REACTION

Still further proof that iodine does not cure hyperthyroidism is the phenomenon known as the postiodine reaction. Examples of this are numerous. It is well recognized that if the medication is discontinued at the end of the remission, reaction to the original rate or even to a higher rate will occur rapidly. Hence, in clinical use the control by iodine must be continuous before, throughout and after the operation.

In the case illustrated in chart 5, a remission in a patient with adenomatous goiter with hyperthyroidism had brought the metabolic rate in fourteen days from  $+38$  per cent to  $+16$  per cent, because of the severity of the cardiac condition, operation was postponed, and the iodine was discontinued, during the next twenty-seven days, the metabolic rate rose to  $+60$  per cent and then spontaneously fell to  $+50$  per cent. Another example is afforded by the course in the case of Miss M. F. The metabolic rate fell from  $+82$  per cent to  $+21$  per cent under treatment with Lugol's solution, after which ligation was performed. Iodine was then discontinued in order that the effect of this operation might be observed. A postiodine reaction then occurred with a rise of rate in ten days from  $+21$  per cent to  $+53$  per cent, the pulse rate rising from 82 to 113.

It is not so well recognized that when iodine administration has been associated with a recurrence or continuation of mild hyperthyroidism, or

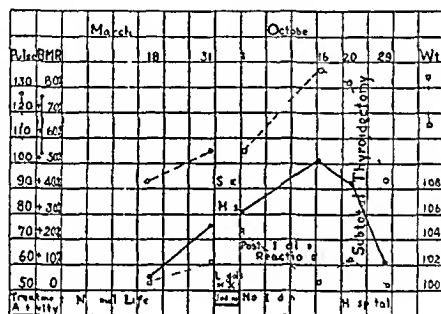


Chart 6—Postiodine reaction after six months of iodine. Note tachycardia and loss of weight. Miss B. H., aged 18, pathologic report acute hyperthyroidism, incorrect procedure.

is without apparent effect, that if it is then stopped, a temporary exacerbation of symptoms and rate occurs, which may be severe. Four examples of the postiodine reaction during recurrence or in the absence of remission were given in the previous paper,<sup>2</sup> two typical examples, one studied deliberately, are given here. Furthermore, the cases illustrated in charts 8 and 9 are in accordance with the history of postiodine reactions.

In the case illustrated in chart 6, the presence of mild hyperthyroidism was suspected because of tachycardia, without iodine the metabolic rate rose from  $+8$  per cent to  $+27$  per cent, then, with the mistaken idea that small doses of iodine would abort this mild attack, 10 minims (0.6 cc.) a day of Lugol's solution was given, at the end of six months, the rate of thyrotoxicosis was about the same. Iodine was then stopped and during the next fifteen days hyperthyroidism increased to such an extent that the basal metabolism rate was  $+50$  per

cent, the tachycardia over 130, and the weight gained during the preceding six months was abruptly lost. The disease passed from a condition of partial control to one of unchecked activity.

A young girl with a colloid goiter had been treated with iodine at home for two months (chart 7). When the patient entered the hospital, Lugol's solution was ordered immediately, and with rest, the rate fell from +90 per cent to +56 per cent, during the next two weeks no material change occurred, although there was a marked gain in weight. It was then decided to allow the postiodine reaction to occur in the hope that after it had run its course, an iodine remission could be produced. When the medication was stopped, the metabolic rate rose during the next twenty-seven days from +56 per cent to +74 per cent, and there was a corresponding tachycardia. The rate then fell spontaneously to +52 per cent, when iodine medication was again started, a remission occurred, the rate dropped to +23 per cent. Subtotal thy-

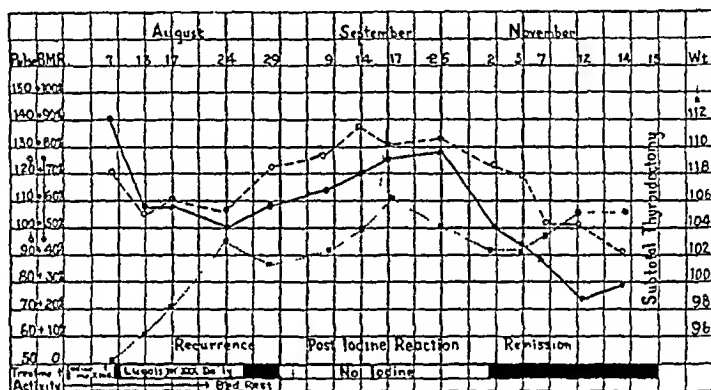


Chart 7—Postiodine reaction at the end of recurrence. Complete self-limited course of postiodine reaction shown. All three stages of iodine effect in hyperthyroidism illustrated. Miss E. A., aged 16, acute hyperthyroidism, pathologic report: colloid goiter and hyperplasia.

roidectomy was then successfully accomplished. This case constitutes further demonstration of the postiodine reaction, bringing out especially that it may occur even if iodine is at the time unable to lower the metabolic rate materially.

Another example illustrates the possibility of the postiodine reaction after prolonged iodine control. On examination, Mr. G. D. presented marked exophthalmos, but a metabolic rate of +12 per cent. He had received iodine for six months before this, it had been started as treatment in acute hyperthyroidism. Unfortunately, the diagnosis was questioned, and the medication stopped, seven days later, the metabolic rate had risen to +53 per cent, with corresponding tachycardia.

Experience with a case of induced hyperthyroidism described below indicates that the thyroid condition in iodine hyperthyroidism is not an

exception to this rule, postiodine reaction occurs when the iodine is stopped, even when it has been responsible for the presence of hyperthyroidism. It may be stated as a general rule, experimentally demonstrated and repeatedly observed, that when a patient with hyperthyroidism has received iodine medication, whether or not the remission or recurrence is then in progress, an increase in metabolic rate and an exacerbation of symptoms occur during the succeeding days or weeks when the administration of iodine is suddenly stopped.

#### THYROTOXIC CRISES

Perhaps the most dramatic use of iodine in hyperthyroidism is in the control of severe thyrotoxic crises. It was for this especially that Plummet introduced the administration of large doses. If iodine is used consistently and continuously before, during and after the opera-

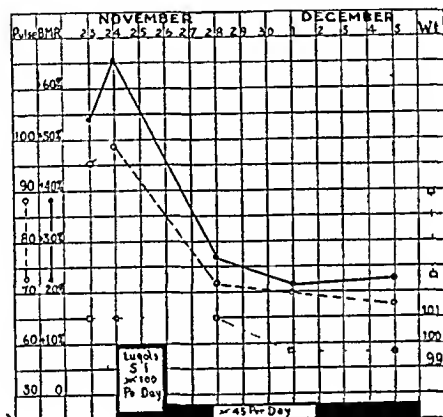


Chart 8—Control of thyrotoxic crisis occurring as a postiodine reaction in a patient with an adenomatous goiter with iodine hyperthyroidism. Mrs. M. S., adenomatous goiter, gastric crisis.

tive period, it is rare to see these crises. In two instances in which iodine was not given postoperatively, crises occurred. Apparently, crises which are essentially postiodine reactions occur immediately after the operation. The optimal period over which to continue iodine medication after the operation is not definitely known, it is about two or three weeks. Segall and Means<sup>5</sup> have shown that the immediate effect of subtotal thyroidectomy is complete in ten days.

A recent example of what Dr. Arnold S. Jackson has emphasized as iodine hyperthyroidism<sup>6</sup> is given in the following case (chart 8). It again shows the postiodine reaction.

5 Segall, H. N., and Means, J. H. Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, Daily Basal Metabolism and Pulse Observations, *Arch. Surg.* 8:176 (Jan.) 1924.

6 J. Jackson, A. S. Iodine Hyperthyroidism, *Am. J. M. Sc.* 170:271 (Aug.) 1925.

Mrs M S, aged 50, had vomited constantly for five days, she complained of abdominal distress, she had lost 25 pounds (11 Kg) during the previous seventeen days. Until then, she had been taking iodine tablets because of difficulty in swallowing, said to be caused by an inward goiter, she had begun this treatment eight months previously. Physical examination revealed an emaciated, nervous woman, exophthalmos not present, a slightly enlarged thyroid gland, a pulse rate of 90, weight, 101 pounds (46 Kg), blood pressure, systolic 180, diastolic 96. The basal metabolic rate was +54 per cent, the next day it was +66 per cent. The patient was observed in the hospital for three days, she vomited frequently and was able to take only small amounts of liquid. She was then given 100 minims (6 cc) of Lugol's solution by rectum in two doses, and during the next day, ten doses of 5 minims (0.3 cc) of Lugol's solution by mouth, all of which she retained. During this day she did not vomit, and ate light food, on the next day she ate three meals, including meat, potatoes and pumpkin pie. Fifty minims (3 cc) of Lugol's solution were given on this

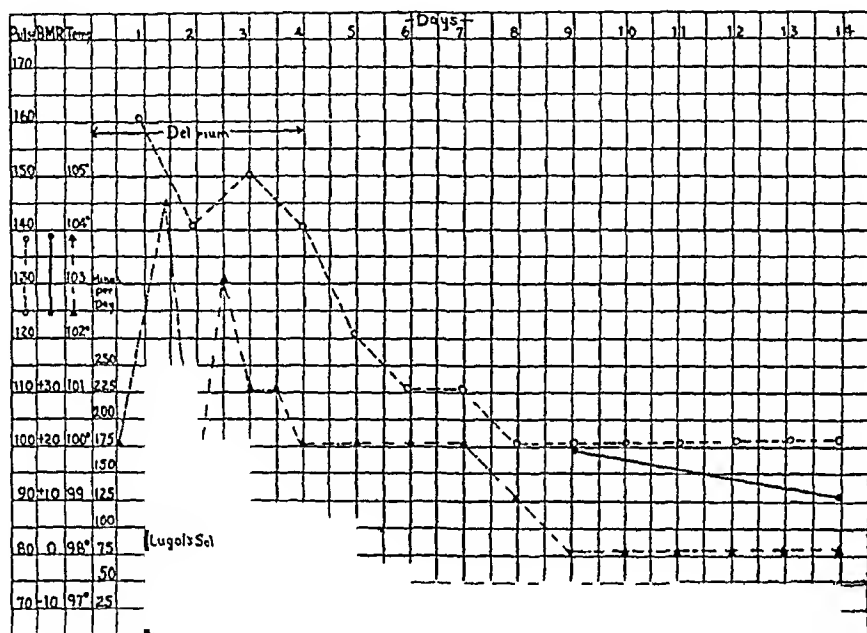


Chart 9—Control of acute thyrotoxic crisis occurring as a postiodine reaction after complete remission. Large dosage of Lugol's solution

second day, thus in forty-eight hours she received 200 minims (12 cc) of Lugol's solution. Two days later the metabolic rate was +27 per cent. Subtotal thyroidectomy was later successfully accomplished. The pathologic report was "colloid goiter with moderate diffuse adenomatous growth."

A similar but more striking example of a violent thyrotoxic crisis occurring as a postiodine reaction may be cited in the following case.

Mr L O, a young white man, was admitted to the hospital in a delirious condition on June 16. The parents said that he had had a goiter for several years. In February he became nervous, and his eyes began to bulge. It is evident from this history that hyperthyroidism was already in progress. A metabolic rate determination was made on May 17. This was +25 per cent. Five grains (0.3 Gm) of potassium iodide was taken three times a day from May 18 until after the second metabolic rate measurement on May 28. This was -9 per cent. The administration of iodine was then stopped. On June 13 the patient became

dizzy, had a headache and was nauseated. During the next three days, he became progressively more restless and irritable. When first seen he was delirious and needed restraint. The pulse rate was 160 and the temperature 104.5 F. The skin was hot, dry and dull red. The eyes were closed, but the eyeballs bulged. There was diffuse, symmetrical, rapidly pulsating goiter, having a thrill and bruit. The lungs were clear. The precordium was heaving, the heart rhythm was regular, gross murmurs were not present. The abdomen was normal, the bladder was distended. Two hundred and forty-five minims (15 cc) of Lugol's solution were given by mouth during the first twenty-four hours, morphine was used to control restlessness, repeated ice packs rapidly reduced the temperature. Large quantities of orange juice, lactose and fluids were given. After four days of delirium, the patient gradually became more quiet and at the end of a week he was completely rational. He then exhibited exophthalmos goiter which still had a bruit, and slight tachycardia, there was little tremor. On the ninth day, the first metabolic rate determination was only +19 per cent. The course and dosage of Lugol's solution is shown in chart 9.

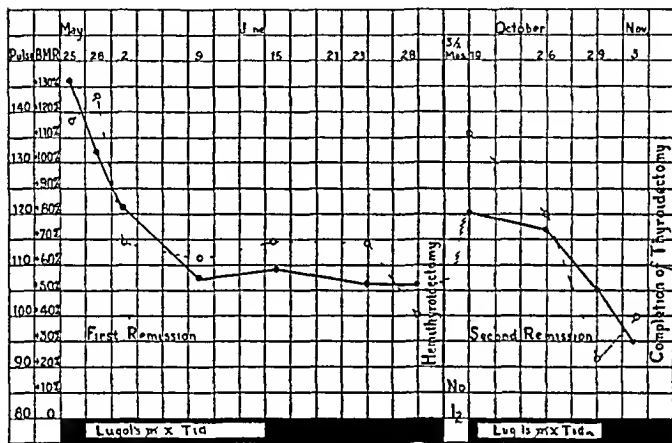


Chart 10—Severe hyperthyroidism, beneficial use of iodine in two periods. Mr. G. E., severe exophthalmic goiter.

Apparently this young man had had mild hyperthyroidism, with an old colloid goiter, fifteen grains (0.9 Gm.) a day of potassium iodide produced marked complete remission to -9 per cent. The iodine medication was then abruptly discontinued, and postiodine reaction began, in which the disease reached maximum severity.

Lugol's solution can be given with benefit in the most severe cases of hyperthyroidism. The progress of the case illustrated in chart 10 is of interest. The first remission from +132 per cent to +55 per cent occurred in fourteen days. Because of operative difficulty, only hemithyroidectomy could be performed. The patient was wisely discharged without iodine, since even though the postiodine reaction would occur, a second remission before the final operation might then be obtained. This proved to be the case. On return, the metabolic rate had risen from +52 per cent to +80 per cent, but on administration of iodine,

it again fell to  $+28$  per cent, with a fall of pulse rate from 135 to 100. The pathologic report was, "Marked hyperplasia."

A patient who had exceptionally severe cardiac dysfunction reacted well to iodine, as indicated in chart 11. The gain in weight was not due to edema. The course of the disease in this patient was that of adenomatous goiter with hyperthyroidism. There was no definite time of onset. For years the patient had had dyspnea on exertion, and hypertension was marked. There was, however, a slight exophthalmos. Remission under Lugol's solution was complete. Pathologic report was, "Fetal adenomas with beginning differentiation."

To summarize: (a) Postoperative thyrotoxic crises do not occur when the administration of iodine is continuous during and for at least ten days after the operative period, (b) in severe crises, large doses of Lugol's solution are effective, (c) iodine has the usual action

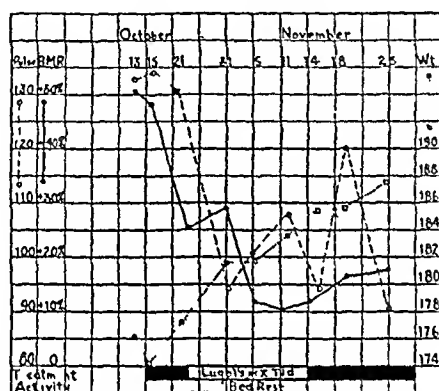


Chart 11—Complete remission with excessive cardiac pathologic change. Mr. G. L., chronic hyperthyroidism, fibrillation, pathologic report: fetal adenoma, patient not operated on, died.

in hyperthyroidism, characterized by excessively high metabolic rate or by severe cardiac disease.

#### COMMENT

If it is true, as the clinical data offered indicate, that iodine does produce a temporary remission in all varieties of hyperthyroidism, a similarity of essential pathogenesis in all these varieties seems probable. Viewed in this light there is no qualitative difference between the mechanism producing hyperthyroidism in adenomatous goiter and that in exophthalmic goiter. The obvious clinical differences are only symptomatic, being dependent on difference in degree and in duration of hyperthyroidism.

Furthermore, if it were true that there was an essential difference between the various clinical types of hyperthyroidism, it might be expected that one of these would be resistant to iodine. The reverse is true. No single type of hyperthyroidism is alone resistant. Patients

with all the varieties of hyperthyroidism that I have observed have failed to give the iodine remission, from those with cases characterized by exophthalmos and hyperplasia to those with cases characterized by adenomatous goiter

In relation to the induction of hyperthyroidism by iodine it may be stated that in an examination of 125 patients with hyperthyroidism who had been given iodine, not a single instance of immediate increase in symptoms was found. On the other hand, under prolonged administration increasing symptoms were the rule, and postiodine reactions were common. One way in which iodine appears to induce hyperthyroidism is by suppressing temporarily an already present disease (remission), even though mild and associated with an adenomatous gland (6, chart 3), the gland then forces a return of the primary condition (recurrence) perhaps even in more severe form (4, chart 6). When the iodine is stopped, there is a rapid flourishing of the disease (postiodine reaction, chart 10).

From the experiments of Starr, Segall and Means<sup>7</sup> on thyroid feeding, and on injections of thyroxin by Sturgis<sup>7</sup> in relation to the site of action of iodine, it seems evident that the inhibiting action takes place in the thyroid gland and not in the general body tissues. This is further supported by the recent successive removals of thyroid tissue in patients with hyperthyroidism under iodine medication by Rienhoff<sup>8</sup>.

The deductions in regard to administration of iodine in hyperthyroidism, to be made from the clinical data illustrated, are as follows:

- 1 If operation is to be performed, iodine should be administered as described, for from ten to fourteen days, with the hope that a remission will occur.
- 2 If iodine medication is started, it should not be discontinued until the immediate effect of subtotal thyroidectomy is complete.<sup>5</sup>
- 3 If iodine has been administered for a long time before observation, (a) it should be continued in order to prevent the postiodine reaction, this is true even if iodine is held responsible for the existence of the present hyperthyroidism, or (b) the administration of iodine may be stopped, the postiodine reaction allowed to pass and iodine again given in the hope that a remission will then take place.
- 4 If a severe thyrotoxic crisis is present either before or after operation, relatively enormous doses of iodine are indicated.

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7 Sturgis, C. C. Personal communication to the author.

8 Rienhoff, W. F., Jr. Histological Changes Brought About in Cases of Exophthalmic Goiter by the Administration of Iodine, *Bull. Johns Hopkins Hosp.* **37** 285 (Nov.) 1925.

## CONCLUSION

The course of hyperthyroidism under iodine medication is characterized by remission and recurrence during the administration of iodine and by a reaction, which may be extreme, after the iodine is discontinued, hence, the prolonged treatment of patients who have hyperthyroidism with iodine in dosage sufficient to produce these effects is without final benefit

# CARDIAC CHANGES SUBSEQUENT TO EXPERIMENTAL AORTIC LESIONS \*

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In an attempted analysis of the complicated conditions found in organic heart disease in man, studies of experimental lesions in the laboratory animal are of recognized value. The great value of the experimental procedure is the production, at least initially, of a single restricted lesion, a knowledge of the date of its incidence and the possibility of subsequent unrestricted observation. Although a large amount of work has been done in studies of both the clinical condition occurring in man and the functional and anatomic sequences of experimental lesions, we are far from a satisfactory understanding or agreement in regard to certain of the most fundamental questions. Two of the more important of these considerations are the cause and progress of the hypertrophy of the cardiac muscle which accompanies most cases of organic heart disease and the alterations frequently observed in the electrocardiogram in clinical cases. The series of experiments described in this article was undertaken with the hope of adding to the knowledge concerning these two particulars.

## SIZE OF HEART IN AORTIC STENOSIS AND REGURGITATION

Rosenbach<sup>1</sup> produced aortic regurgitation and, in a few instances, mitral regurgitation in rabbits and found evidence of dilatation and subsequent hypertrophy. The hearts were observed beating in situ, and measurements of the thickness of the ventricle were made and compared with those of normal controls. Muller<sup>2</sup> came to similar conclusions by comparisons of heart and body weight. Romberg and Hasenfeld<sup>3</sup> recorded a heart weight body weight ratio of 0.00219 in rabbits with aortic regurgitation as compared with 0.00195 in a series of controls. The left ventricle was the seat of the principal hypertrophy as determined by the comparative weights of the two ventricles. The right ven-

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1 Rosenbach, O. Artificielle Herzklappenfehler, *Arch f exper Pathol u Pharmacol* **9** 1, 1878

2 Muller, F. Die Massenverhältnisse des menschlichen Herzen, Hamburg and Leipzig, 1883

3 Romberg, E., and Hasenfeld, A. Ueber die Reservekraft des hyperthrophischen Herzmuskel, *Arch f exper Pathol u Pharmacol* **39** 332, 1897

tricle was involved only in high grade insufficiency Stadler<sup>4</sup> studied the hearts of four rabbits with aortic regurgitation, two with aortic stenosis and six with tricuspid regurgitation. The duration of the lesion varied from thirty to one hundred and seventy days. In each case, heart weight/body weight ratios, weight of auricles, ventricular septum and each ventricle were given and compared with those of normal rabbits of the same body weight. In aortic stenosis and regurgitation the greatest increase in weight occurred in the left ventricle and septum, although some animals showed an increase in the right ventricle and auricle as well. In the animals with tricuspid regurgitation, the right ventricle was larger and the left ventricle definitely smaller than those of the controls. On histologic examination, evidences of hypertrophy in the former and of atrophy in the latter were found. Wolfer<sup>5</sup> obtained a heart weight/body weight ratio of 0.00209 in a group of normal rabbits, and of 0.00275 in seven animals after aortic stenosis. All of the latter exceeded the normal average, and two, the normal maximum. The ratio between the weight of the left and the right ventricles was 1.7 in the normal series and 1.86 in the series of aortic stenosis. He also studied the hearts of seven animals with aortic regurgitation and found a heart weight/body weight ratio of 0.0021 and left/right ratio of 1.82. Schliephake<sup>6</sup> found only slight variations in the weight ratios in four rabbits with aortic regurgitation as compared with those of ten controls. Stewart<sup>7</sup> studied experimental aortic regurgitation in twenty dogs and compared weight ratios with twenty controls. Heart weight/body weight ratio in the aortic regurgitation series was above the normal average in 90 per cent and above the normal maximum in 85 per cent. He found that the hypertrophy affected all chambers of the heart, although the left ventricle increased in absolute weight more than the other chambers. Hypertrophy developed with surprising rapidity, being evident within a week after the production of the lesion. Herrmann<sup>8</sup> more recently has published extensive series of measurements of heart weight in normal dogs and in dogs with experimental aortic regurgitation. He compared heart weight/body weight ratios and the relative weights of the two ventricles to body weight and to each other. His principal results are summarized in table 3 and are compared with similar determinations made by us. In seventy dogs with aortic regurgitation, all but four

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4 Stadler, E. Experimentelle und histologische Beiträge zur Herzhypertrophie, *Deutsches Arch f klin Med* **91** 98, 1907.

5 Wolfer, P. Experimentelle Studien zur Reservekraft des hypertrophischen Herzens, *Arch f exper Path u Pharmacol* **68** 435, 1912.

6 Schliephake, E. Die Veränderung des Ek nach künstlichen Aorteninsuffizienz und Hypertrophie des linken Herzens, *Ztschr f klin Med* **97** 96, 1923.

7 Stewart, H. A. An Experimental Contribution to the Study of Cardiac Hypertrophy, *J Exper Med* **13** 187, 1911.

8 Herrmann, G. R. Experimental Heart Disease, *Am Heart J* **1**:485, 1926.

exceeded the normal average heart weight body weight ratio established in 200 normal dogs, and fifty were above the upper normal range. In the relation of the weights of the two ventricles (left right ratio) there was evidence of preponderant hypertrophy of the left ventricle. All but five hearts exceeded the normal average ratio, while forty-three exceeded the upper normal range. In contrast to Stewart's <sup>5</sup> results, Herrmann did not find any evidence of hypertrophy in less than nineteen days. The maximum hypertrophy was obtained in approximately one hundred and ten days.

#### METHODS

In the present series of experiments the progress and extent of cardiac enlargement following experimental stenosis and regurgitation in dogs were studied by the determination of the area of the roentgen-ray silhouette of the heart taken at a distance of 1 meter from target to film and correcting for distortion. Extensive experience both in the experimental animal and in man has shown that the area of the frontal plane silhouette is the most accurate and reliable of the various possible measurements of the heart shadow. The dog's heart is suspended in the chest wall above the level of the diaphragm, and a clear outline, including the lower border is obtained, which makes the determinations of the area of greater accuracy in dogs than in man. Repeated observations in the same animal in this and preceding work in which this method was used have assured us of the remarkable constancy of the area of the cardiac silhouette in the same animal under the same conditions at different times. Such variations and errors in measurement fall well within a  $\pm 5$  per cent range. The roentgenographic method has the advantage that there is the possibility of numerous observations during the progress of the condition as compared with a single terminal observation when the weighing method is employed, and that a normal is determined in each animal rather than an average curve with variations established from a large number of animals. The method of comparative weight appears to have the inherent disadvantage of a wide range of normal variations, especially in dogs. This is true in a single series made on animals presumably derived from a restricted territory and measured by the same technic, and becomes greater when the standards established by different observers are compared. In Herrmann's extensive normal series, the heart weight body weight ratio and the left to right ventricle weight ratio vary through a  $\pm 25$  per cent variation and a  $+ 17$  per cent to  $- 25$  per cent variation, respectively, from the average figures. According to this standard, it would be possible for a left ventricle, initially at the lower limit of normal, to increase 50 per cent of its original weight before passing the upper limit of normal, assuming that the right ventricle remained unchanged in weight. The principal disadvantages of the roentgen-ray method are that it does not distinguish between dilatation

and hypertrophy, and that it fails to show with accuracy which part of the heart is most affected. We have also made observations of the terminal weight in ten animals in the stenosis series and in eight in the regurgitation series.

The first series of experiments comprises nineteen dogs in which an aortic stenosis was produced by a constricting band. The third or fourth rib on the right side was resected under insufflation anesthesia, the pericardium opened and a band placed around the aorta immediately above the valves. The band was tightened until the vessel was obviously compressed and a distinct thrill developed on palpation. Metal bands of aluminum or German silver were used at first, but it was found that these had a tendency to erode the walls of the aorta, and elastic bands were employed subsequently. Ligatures of catgut were used in a few experiments but seemed to possess no advantage. Attempts were made to produce stenosis in twenty-eight animals. Two died from difficulties encountered in the operative procedure, one died from pneumonia on the ninth day following the operation and seven died within a period of from six hours to sixteen days following the operation, apparently as a result of too great a constriction of the vessel, autopsy, at least, failed to reveal any other cause of death. Eighteen animals recovered completely from the immediate effects of the operation and were observed for periods varying between twenty-eight and one hundred and forty-eight days. A roentgen-ray determination for the size of the heart and electrocardiograms of the three standard leads were made before and at varying periods subsequent to the operative procedure. In most cases two leads were recorded simultaneously to insure more accurate estimation of the electrical axis. At the end of the period of observation the animals were killed, autopsy was performed, the position of the band was noted and the presence of a constricted orifice was verified.

In fifteen dogs, experimental aortic regurgitation was produced by the introduction of a valvulotome through the right carotid artery. In all but two animals one valve leaflet alone was cut, in two (nos 25 and 26) two valve leaflets were bisected. Roentgen-ray and electrocardiographic observations were made as in the stenosis series. The periods of observation varied from seventy to two hundred and ten days.

#### EXPERIMENTAL WORK

*Experimental Aortic Stenosis*—So far as we know, the only previous experiments of a similar type in this lesion is the series of seven rabbits of Wolfer<sup>5</sup> and the two rabbits of Stadler<sup>4</sup> with observations for terminal weight. The roentgen-ray results for area and terminal weight in the present series of experiments are summarized in table 1. The figures following the column recording the day of observation give the area of the cardiac silhouette expressed in square centimeters. Exam-

TABLE 1—*Aortic Stenosis*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Average
Before operation	36	47	49	42	40	38	35	41	48	38	60	30	49'	48	38	47	42	45	43	
After operation	52	57	49				38		47											+18 %
1 days	55																			+ 6 %
7 days		54	52	41	40															
10 days	62	51																		
14 days		52	50									33				47			52	+ 8 8%
21 days		51	48	42										54						
28 days		57	52	42						38		28	53	51	38	51	47	45	51	+ 8 4%
35 days		56	50	41	41	39							53	51						
42 days		57	50	41																
49 days		58	49	41			44	45					53							+11 %
56 days		57										31			43		55	49		
63 days		57									58								52	
70 days			50	44				47				32	51	50		51	55			
77 days		56	49	42																
84 days		59		44	42	40			46			32				51				
106 days			51	47														52	51	
120 days						38														
134 days			51																	
148 days			54	47												50				
Percentage change		+26	+10	+12	+5	0	+26	+15	—4	0	—3	+7	+4	+4	+13	+7	+31	+16	+18	+10 5
Body weight		8 62	9 50	8 40	8 66	8 34	5 2	9 2	11 2	7 76	6 9	6 42	11 84	11 4	8 54	10 5	11 0	11 6	11 7	
VW/BW*		810	715	668				772				571	505	519	602	621	622			642
LVW/BW*		550	425	447				576				317	318	334	364	390	334			401
L/R		2 17	1 60	1 86				2 01				1 27	1 71	1 82	1 53	1 78	1 16			1 69

\* Decimal point and first two zeros omitted 810 should read 00810

ination of these data shows that there was little or no apparent change in cardiac size in five experiments, while a definite increase occurred in the remainder. The average for the whole group was an increase of 10.5 per cent of the original area. The greatest increase observed was 31 per cent. The final column of the table gives the average percentage increase above the normal at different periods subsequent to the operative procedure. These figures were obtained by determining the percentage change in each case recorded on the days noted and making an arithmetic average. A marked cardiac enlargement was noted in three of four animals observed immediately after the operative procedure. We believe this represents an initial dilatation from which the heart may partially or entirely recover before hypertrophy begins. It shows more

TABLE 2—*Aortic Regurgitation*

Experiment	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	Aver,
Before operation	69	55	61	57	57	55	59	36	38	41	35	52	41	39	44	
After operation	70	65	67	60	53	52	41	38								+5.1
2 days	74	58	65			55										+2.1
7 days	66	54		62	56	55	44									+2.5
14 days	69		70		51	49			38							-1.4
21 days		54	73	57	54	46				45						+1.7
28 days	71			63	50				40							+2.5
35 days	69	62	70	59	51	47										+2.5
42 days			70	55						49						+8.9
49 days	75	65		55												+7.8
56 days		60	70			49										+8.9
63 days	75		73		55					56						+15.2
70 days		63		62		57				60						+18.3
77 days	75	59	76		61											
84 days		63	75	60												
93 days	80	69	80													
130 days	85						51	50			48	57	43	39	51	+17.5
180 days					64	60										
210 days		69	84	72												
Per cent change in area	+19	+25	+38	+26	+12	+9	+31	+39	+5	+46	+37	+10	+5	0	+16	+22
Body weight	14.4	12.7	14.2	11.9	13.2	9.9	9.05	8.9								
HW/BW	862	855	951	823	746	933	819	784								859
VW/BW	753	718	808	761	602	796	703	661								723
LVW/BW	402	408	517	445	352	461	403	412								425
L/R	1.17	1.32	1.77	1.40	1.41	1.31	1.34	1.60								1.41

clearly in the larger number of animals observed at this stage in the aortic regurgitation series. In one animal (exper. 1) continued dilatation occurred, and the animal died on the sixteenth day. The subsequent enlargement, to be interpreted probably as hypertrophy, develops slowly in most animals and appears to be usually complete at approximately the sixth week.

*Experimental Aortic Regurgitation*—Data concerning 10-centigen-ray areas and observations for terminal weight in the aortic regurgitation series are presented in table 2. Previous 10-centigen-ray studies in this condition are those of Sands,<sup>9</sup> Bazett,<sup>10</sup> and Herimann.<sup>8</sup> Sands employed

<sup>9</sup> Sands, J. Chronic Aortic Regurgitation in Dogs, vi Int. Physiol. Congress, Quart. J. Exper. Physiol., suppl. vol., 1923, p. 215.

<sup>10</sup> Bazett, H. C. Further Observations on Experimental Aortic Regurgitation, Proc. Am. Physiol. Soc., Am. J. Physiol. **72**: 201, 1925.

short exposures (from one to ten seconds) in which the incidence in the heart cycle and the relation to the phase of respiration were determined by simultaneous electrocardiograph and respiratory records. Immediately after and for a period up to two weeks following the lesion, the hearts were longer and narrower. Later the hearts were larger in all dimensions. Bazett found that considerable hypertrophy occurs but develops slowly. Herrmann noted that many of his animals with aortic regurgitation showed evidences of cardiac enlargement on roentgen-ray examination, but he does not present any data. The average percentage changes from the normal at different times are given in the last column of the table and charted in figure 1. Six of eight dogs showed an enlarged heart immediately following the injury to the valves. In two of the four in which this was observed, the initial enlargements disappeared within seven days, in one by the twenty-first day, and in one it apparently

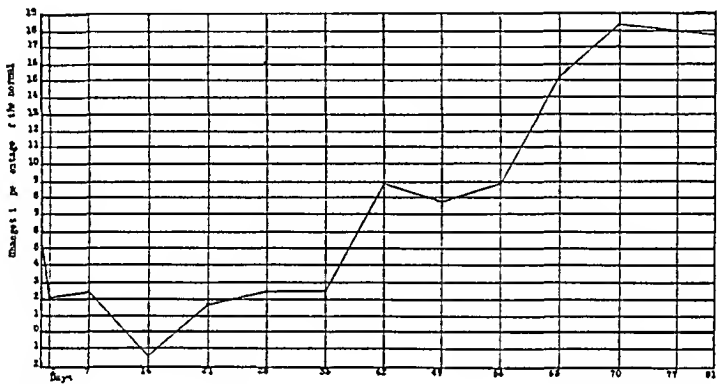


Fig 1—Average changes in size of heart in aortic regurgitation

remained. It seemed possible that heart rate changes following the operative procedure might be of importance in this connection. Meek<sup>11</sup> has shown that the size of the dog's heart is little affected by moderate changes in rate, but that it rapidly decreases in size with a fast rate. In the six hearts showing initial enlargement (19, 20, 21, 22, 25 and 26) heart rate was higher after operation (average percentage increase of 67 per cent) than before in four (19, 20, 23, 25), unchanged in one (21) and slightly decreased in one (22). The greatest initial enlargement observed (exper. 20) was associated with a 33 per cent increase in heart rate. In the two hearts failing to show initial enlargement (23 and 24), the heart rate increased in the former 51 per cent, and in the latter it decreased 17 per cent as compared with the rate before operation. It seems difficult to associate any change in cardiac area observed with changes in heart rate. From the average figures it appears that a second period of enlargement follows the first after approximately two weeks,

11 Meek, W. J. Effect of Changes in Pulse Rate on Diastolic Heart Size, *Am J Physiol* 70:385, 1924

and continues at first rapidly and then more slowly to beyond the hundredth day. The most probable explanation of the results is that the initial enlargement is an initial cardiac dilatation. Later the ventricles in most cases appear to regain their normal tonus, and this is succeeded by enlargement caused by hypertrophy.

*The Electrocardiogram in Experimental Aortic Stenosis and Regurgitation*—Fraser<sup>12</sup> recorded the electrocardiogram during dilatation in rabbits' hearts produced by the injection of spartein and epinephrine hydrochloride. Dilatation of the right side of the heart as determined by roentgen-ray observations, produced increase of the R and decrease of the S wave. Dilatation of the left side produced opposite effects. When both sides were dilated, no change was observed. Schliephake<sup>6</sup> recorded lead II from four rabbits with experimental aortic regurgitation. Q and R increased, especially the former. The T wave at first decreased and then increased as the hypertrophy developed. Sands<sup>9</sup> found that preponderance in the left ventricle was not present even after full hypertrophy developed as a result of aortic regurgitation. Bazett recorded an increase in Q and R waves and a reduction or disappearance of the S wave in all leads, while the duration of the QRS group was increased. Heilmann<sup>8</sup> stated that in the electrocardiogram only one of the seventy dogs with aortic regurgitation in his series showed any significant changes (left preponderance). This occurred in the dog showing the greatest relative hypertrophy of the series.

In clinical aortic regurgitation preponderance of the left ventricle occurs more frequently than in the normal heart. In twenty-one cases of aortic regurgitation with no history or present indications of incompetence, preponderance of the left ventricle was noted in 53 per cent as compared with 24 per cent in a series of 100 clinically normal hearts. It is interesting to know whether this tendency to axis deviation is an early or late change in the progress of the hypertrophy. It is also important to determine by detailed studies of frequent electrocardiograms whether or not any changes occur which are characteristic of early dilatation or hypertrophy.

Electrocardiograms were made by the standard three leads in all animals in both the stenosis and regurgitant series whenever roentgen-ray observations were made. In most cases two leads were recorded simultaneously to insure greater accuracy in measuring the electrical angle. These curves have been further analyzed respecting possible changes in heart rate, PR, QRS and RT intervals and Q, S and T waves in the different leads. The relationship between changes in rate and changes in PR interval were inconstant and apparently were not

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12 Fraser, F. R. Changes in the Electrocardiogram Accompanying Experimental Changes in Rabbits' Hearts. *J. Exper. Med.* **22**: 292, 1915.

significant. The QRS interval was unchanged or slightly decreased in 66 per cent, increased in the remainder. The former showed an average terminal cardiac area of  $+14$  per cent, as compared with  $+6$  per cent in the latter. It is well known that in clinical hypertrophy the QRS interval is frequently increased, especially in the presence of left axis deviation. Our results would indicate that this is not a change characteristic of early hypertrophy. The RT interval, as an approximate measure of ventricular systole, is of interest. It was definitely increased in 55 per cent, and unchanged or slightly decreased in the remainder. Terminal cardiac area was increased, 11 per cent in the former group, 14 per cent in the latter. There thus does not seem to be an association between the length of systole, as thus estimated, and the extent of hypertrophy. The electrical axis was within its normal range at the initial observation in all experiments in both series except in one instance. The animal in experiment 32 showed a deviation of the right axis of  $-178$  degrees, practically unchanged at the terminal observation in this animal. Deviation of the axis seems to be rare in normal dogs as compared with human beings. The average normal angle was  $+64$  in the stenosis series and  $+58$  in the regurgitation series. The range in the two series (excluding the one case of right axis deviation) was from  $+37$  to  $+82$ . The average angle in the stenosis series showed a tendency to shift to the left (from  $+64$  to  $+47$ ) at the terminal observations, but practically no change occurred in the series of aortic regurgitation. Changes in the Q, S and T waves in the three leads were inconstant and apparently without significance. In the stenosis series the sum of the Q waves in the three leads increased in 45 per cent and decreased in 45 per cent. The S waves increased in 33 per cent and decreased in 45 per cent. The duration and size of the T wave in the different leads in normal dogs is extremely variable and inconstant.  $T^1$  and  $T^2$ , as well as  $T^3$  negativity are common, and changes occur from time to time in the same animal without apparent cause. The T wave in the dog fails to have the clinical significance which it appears to have in man. Equally inconstant and insignificant changes occurred in the animals with experimental stenosis and regurgitation.

The degree of cardiac dilatation and hypertrophy encountered in dogs as a result of experimental aortic lesions thus fails to produce any significant change in the electrocardiogram. In order to determine whether or not extreme grades of dilatation in an otherwise normal heart showed any important changes, five additional experiments were performed. In four dogs, acute and massive dilatation of the left ventricle was produced by transient occlusion of the descending thoracic aorta, and in one dog similar transient dilatation of the right ventricle was secured by the rapid infusion (200 cc within ten seconds) of physiologic sodium chloride at body temperature through a large cannula.

into the jugular vein under a pressure of about 80 millimeters of mercury. In the former experiments, the aortic ligature was laid after resection of the rib, and the thorax was closed and normal respiration reestablished before the experimental procedures were performed. Electrocardiograms from the three leads were made in two experiments by three galvanometers recording simultaneously. In the three other experiments, two leads only were recorded. Carotid blood pressure was also recorded. The changes in the electrocardiogram resulting from aortic occlusion with dilatation of the left ventricle or rapid venous infusion with dilatation of the right ventricle were practically negligible. The only effect observed was a slight transient increase in PR and RT intervals. Figure 2 is the electrocardiogram made during a period of aortic occlusion. In two dogs, the same procedure was carried out after the production of an aortic regurgitation, with identical results.

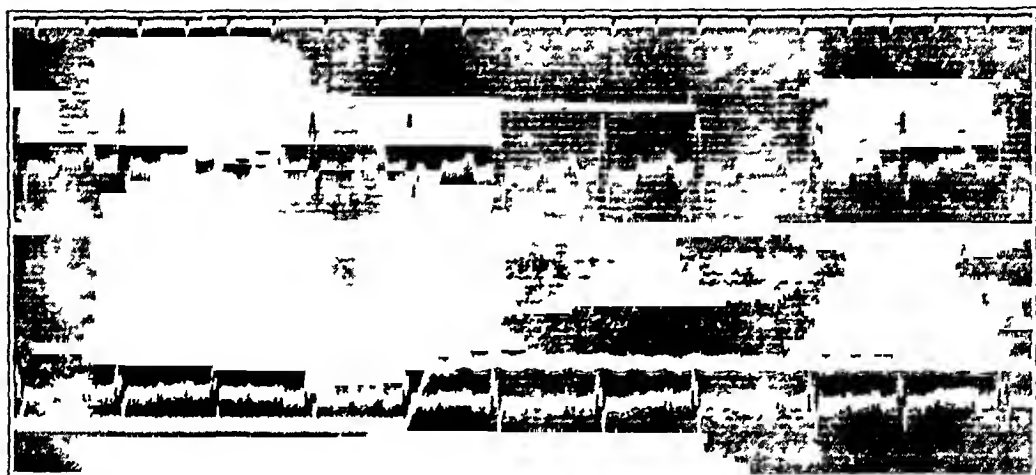


Fig 2—The electrocardiograms (lead 2 upper, and lead 3 lower curve) during temporary occlusion of the descending aorta in a dog. Onset of occlusion marked by rise of marking pen, time in one-fifth of a second intervals.

*Terminal Heart Weight Determinations in Stenosis and Regurgitation*—Determinations of heart weight from ten experiments in aortic stenosis and eight experiments in aortic regurgitation are given in tables 1 and 2. We have, in addition, made similar determinations on seventeen normal animals, and while this series is small compared to Herrmann's data, it represents a normal established under the same conditions and with the same technic as that of the abnormal animals. The technic of separating and weighing the two ventricles was essentially that of Herrmann's. Comparisons of the normal animals with the more important measurements in aortic stenosis and regurgitation are given in table 3. It will be noted that our figures are in most cases lower than those of Herrmann, both for the normal and for the abnormal series, and that less striking differences are established. Probably the two most

important measurements are the ratio of body weight to the weight of the left ventricle (LVW/BW) and the relative weights of the two ventricles (R/L). In the former case, the averages of the two abnormal series exceed the averages of both normal series, but are definitely lower than that of Herrmann's series of aortic regurgitation. In the eighteen animals with stenosis or regurgitation, all exceeded our average normal figure, and twelve exceeded Herrmann's normal average. The right left ratio in our series, however, fails to indicate preponderant hypertrophy of the left ventricle.

#### THE DYNAMICS OF AORTIC REGURGITATION AND THE RESERVE FORCE OF THE HYPERTROPHIED HEART

The usual interpretation of the dynamics of insufficiency of the aortic valves is a regurgitation of blood during diastole with a larger amount of blood and an increased tension in the left ventricle at the end of diastole.

TABLE 3—*Determinations of Heart Weight*

	Heart Weight, Body Weight		Ventricle Weight, Body Weight		Left Ventricle Weight, Body Weight		Right Ventricle Weight Left Ventricle Weight	
	Average	Maximum	Average	Maximum	Average	Maximum	Average	Maximum
Herrmann's normal	798	994	635	872	369	472	1.40	1.72
Present normal			516	630	314	388	1.66	1.79
Aortic stenosis			642	810	401	550	1.69	2.17
Herrmann's series of aortic regurgitation	1,053	1,388	849	1,233	554	814	2.00	3.00
Present series of aortic regurgitation	859	933	723	808	425	517	1.41	1.77

The decimal point and one or two zeros have been omitted except in the figures of the last two columns. Thus 798 should read 0.00798 and 1,053 should read 0.01053.

and an increased contraction of the muscle with an increased outflow during systole. In the light of the modern conception of cardiac activity, the increased contraction is the direct result of the increased initial load on the tension or length of the muscle fiber. Stewart<sup>13</sup> has dissented from this view on experimental grounds. By the use of the ventricular plethysmograph in dogs he found the output practically unchanged as a result of the production of aortic insufficiency, and concluded that the regurgitation of blood was negligible, amounting at the most to a fraction of a cubic centimeter. The hypertrophy of the left ventricle was explained on increased diastolic tension caused by transmission of aortic pressure. This view has also been supported by Zollinger<sup>14</sup> from results from similar experiments, in which the pericardium was used as

13 Stewart, H. A. Experimental and Clinical Investigation of the Pulse and Blood Pressure Changes in Aortic Insufficiency, *Arch. Int. Med.* **1**: 102 (Jan.) 1908.

14 Zollinger, F. Zur experimentelle Pathologie und Therapie der akuten Aorteninsuffizienz, *Arch. f. exper. Path. u. Pharmacol.* **61**: 193 (1909).

a plethysmograph, although he found evidence of increased diastolic filling MacCallum,<sup>15</sup> however, employing a heart-lung preparation in which both the output from the aorta and the output from the ventricle were measured and compared, found that regurgitation plays a prominent part in aortic insufficiency and is sufficient to account for the hypertrophy Wiggers<sup>16</sup> came to essentially the same conclusion from intracardiac pressure measurements and concluded that the increased output is due to an increased and longer systole We have measured the cardiac output by means of a cardiometer in three experiments on dogs before and after the production of an aortic regurgitation In each case the injury to the valve caused a significant increase in output associated with a greater diastolic relaxation The immediate increase in output per beat was 20 per cent, 11.5 per cent and 30 per cent, respectively, an average of 20.5 per cent in the three experiments In order to test the comparative ability of the ventricle to meet a marked increase in load after injury of the aortic valve, measurement of the output during transient aortic compression was made in these experiments In the normal heart, transient occlusion of the descending thoracic aorta causes a decrease in cardiac output associated with the marked rise of aortic pressure central to the point occluded This fall in output is greater in the presence of an incompetent aortic valve than with the intact heart In the three experiments, an average of several trials in each case gave a decreased output per beat as a result of aortic occlusion of 16 per cent, 31 per cent and 13 per cent before and of 50 per cent, 54 per cent and 18 per cent after the production of aortic regurgitation The corresponding percentage reductions for minute volume were 17 per cent, 35 per cent and 13 per cent before and 62 per cent, 53 per cent and 18 per cent after It appears, therefore, that the reserve force of the normal cardiac muscle is exceeded when an overload of this extent is applied to a heart with a defective aortic valve It would seem that the effect of hypertrophy is, at least in part, to add to this reserve and to enable the heart with a valve lesion to meet an overload of considerable magnitude Romberg and Hasenfeld<sup>3</sup> studied the reaction of normal rabbits and compared it with the reaction of rabbits with hypertrophic hearts from aortic regurgitation or stenosis or from injection of spartein and epinephrine hydrochloride, to short periods of asphyxia, sensory stimulation, abdominal massage and clamping the thoracic aorta Although marked differences were noted between different animals, these authors believed that the evidence they obtained pointed to the conclusion that the development of hypertrophy increases the reserve force of the heart

15 MacCallum, W. G. The Changes in the Circulation in Aortic Insufficiency, *Bull. Johns Hopkins Hosp.* **22**: 197, 1911.

16 Wiggers, C. J. The Dynamics of Aortic Insufficiency, *Arch. Int. Med.* **16**: 132 (July) 1915.

with an experimental lesion until it is approximately equal to the normal heart. The same conclusion was obtained by Wolfe<sup>5</sup> in whose work the extent and duration of the rise of arterial pressure on clamping the aorta in thirteen normal rabbits was compared with twenty-five rabbits with hypertrophic hearts subsequent to aortic stenosis, aortic regurgitation and administration of epinephrine hydrochloride. According to Eppinger and Knaffl,<sup>17</sup> starvation for several days preceding this test of cardiac reserve reduces the reserve in the normal heart, and reduces it to a greater extent in the hypertrophic heart resulting from aortic regurgitation. It would seem, therefore, that while hypertrophy increases the reserve and the ability of the muscle to meet an increased total amount of work, the hypertrophic muscle is more susceptible to disturbances of its nutrition than the normal muscle.

#### MYOCARDIAL CHANGES IN CARDIAC HYPERTROPHY

Two divergent views regarding the nature of the process in hypertrophy of cardiac muscle are found in the literature. The more prevalent one is that the process is primarily a work hypertrophy stimulated by mechanical conditions of load. The other view is that hypertrophy is the result of a progressive inflammatory process caused by a pathologic nutritive stimulus. The latter view has been supported particularly by Albrecht<sup>18</sup> on the basis of observations made on human hearts. The reports derived from the study of experimental hypertrophy, on the other hand, incline to the former view. Tangl<sup>19</sup> compared the cross diameter of the muscle cells in the hearts of normal rabbits of different body weights and in hypertrophic hearts resulting from experimental aortic regurgitation. He found that the diameter of the fiber increased from 5.57 to 15.33 microns with body weight from 610 to 2,600 Gm., while in hypertrophic hearts a similar relationship existed in which the range in cross diameter was from 14.24 to 20.17 microns. He therefore compares hypertrophy with physiologic growth of the muscle. Most workers believe that the hypertrophy as well as the normal growth of the heart is due to enlargement of the individual fiber, and that mitosis does not occur. This enlargement is ascribed to increase of the fibrillae by some observers, to the sarcoplasm by others. With the increase in the size of the fibers, several observers have noted a frequent but apparently not invariable increase in connective tissue. Stadler<sup>4</sup> ascribes the increase of connective tissue to the mechanical stimulus of dilatation and the increase in size of the fiber to the mechanical stimulus of increased

17 Eppinger, H., and Knaffl, E. Ueber Herzinsuffizienz, *Ztschr. exper. Path. u. Therap.* **5**: 77, 1909.

18 Albrecht, E. *Die Herzmuskel und seine Bedeutung für Physiologie*, Berlin, 1903.

19 Tangl, F. Ueber die Hypertrophie und des physiologische Wachstum des Herzens, *Virchows Arch. f. Path. Anat.* **116**: 432, 1889.

work Eight of the hearts from our series of aortic regurgitation have been examined for us by Dr E M Medlar of the Department of Pathology of the University of Wisconsin All showed a definite enlargement of the fibers of the left ventricle and septum The outer wall of the right ventricle usually showed some hypertrophic cells, but less marked and less extensive than in the left ventricle There was no evidence of degenerative changes in the heart muscle nor of increase of fibrous tissue in any instance

#### CONCLUSIONS

1 Experimental aortic stenosis and insufficiency in dogs is usually associated with a gradually developing cardiac hypertrophy

2 This hypertrophy is preceded by a stage of initial dilatation, usually passing off in part or completely within a few days

3 Aortic insufficiency is associated with regurgitation of blood into the left ventricle and an increased diastolic widening of this chamber

4 The heart with aortic insufficiency before hypertrophy develops fails to react as effectively to an overload as does the normal heart

5 There are no electrocardiographic changes characteristic of the early dilatation or hypertrophy subsequent to aortic lesions Even extreme degrees of dilatation in the normal heart fail to cause significant changes in the electrocardiogram

6 The histologic changes following aortic regurgitation are those characteristic of simple hypertrophy without evidence of degenerative processes in the cardiac muscle

We have known that Dr H C Bazett of the University of Pennsylvania was carrying on a series of observations closely paralleling our own Through the courtesy of Dr Bazett there has been an interchange of manuscripts and we wish to express our appreciation of this The principal difference in our conclusions appears to be the question of the occurrence of an early enlargement subsequent to aortic regurgitation We are unable to suggest the reason for this difference in experimental results, and it would appear that further work on this important question is desirable We should also like to thank Dr E M Medlar of the Department of Pathology of the University of Wisconsin for making the histologic examinations for us

# CHRONIC ACIDOSIS IN RABBITS AND IN DOGS

WITH RELATION TO KIDNEY PATHOLOGIC CHANGE \*

BEATRICE CARRIER SEEHAL, M D

BOSTON

Change in the ability of the kidney to eliminate acids has been recognized as one of the fairly constant symptoms of renal disease. Palmer and Henderson<sup>1</sup> report an abnormally high acidity of the urine caused by a decrease of urinary ammonia in patients with nephritis usually of the glomerular type. The same investigators,<sup>2</sup> also Sellards,<sup>3</sup> Hosslin,<sup>4</sup> and Peabody,<sup>5</sup> find that the amount of alkali which must be ingested before the urine becomes alkaline is increased in nephritis. Sellards reports that this is particularly true in interstitial renal injury. Austin and Cullen<sup>6</sup> review the literature and draw the conclusion that nephritis gives rise to a disturbance of the acid base equilibrium, and that it may lower both the alkali reserve and the plasma  $p_H$ .

These investigators and many others, while recognizing the constant appearance of a disturbed acid excretion, have supposed that this was a consequence of the renal damage. Fischer,<sup>7</sup> on the other hand, believes that acid elimination may play an etiologic rôle in nephropathologic change. He supports his theory by experiments in which he injects acid intravenously in rabbits and finds albumin and casts in the specimens of urine in a few hours. Other work of this nature has been reported as far back as 1878, when Kobert<sup>8</sup> found that 5 per cent phosphoric acid given to dogs and rabbits either by stomach tube or by intravenous injections resulted in albumin, casts and even blood in the urine.

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\* From the Department of Pathology, Harvard University Medical School

1 Palmer, W. W., and Henderson, L. J. A Study of the Several Factors of Acid Excretion in Nephritis, *Arch Int Med* **16** 109 (July) 1915

2 Palmer, W. W., and Henderson, L. J. Clinical Studies on Acid-Base Equilibrium and the Nature of Acidosis, *Arch Int Med* **12** 153 (Aug) 1913

3 Sellards, A. W. The Essential Features of Acidosis and Their Occurrence in Chronic Renal Disease, *Bull Johns Hopkins Hosp* **25** 141 (May) 1914

4 Hosslin, Rudolf. Ueber die Abhängigkeit der Albuminurie vom Sauregrad des Urins und über den Einfluss der alkalizufuhr auf Acidität, Albuminurie, Diurese und Chloridscheidung, sowie auf das Harnammoniak, *Deutsches Arch f klin Med* **105** 147 (Dec) 1911

5 Peabody, F. W. Clinical Studies on the Respiration. II. The Acidosis of Chronic Nephritis, *Arch Int Med* **16** 955 (Dec) 1915

6 Austin, J. H., and Cullen, G. E. Hydrogen Ion Concentration of the Blood in Health and Disease, *Medicine* **4** 275 (Aug) 1925

7 Fischer, Martin H. Edema and Nephritis, New York, John Wiley & Sons, 1915

8 Kobert, E. R. Ein Beitrag zur Phosphosäurewirkung, *Schmidt's Jahrb* **179** 225, 1878

Ewing<sup>9</sup> obtained albumin and hyaline casts in fifty-two hours in a rabbit that had received 2.16 Gm hydrochloric acid subcutaneously. Microscopically, he found granular and hydropic degeneration of the renal tubule cells. MacNider<sup>10</sup> conducted a series of four hour experiments in which dogs received two doses of two-tenths normal hydrochloric acid, 5 cc per kilogram. Albumin and casts appeared in the urine. Microscopically, the kidneys showed injury to the convoluted tubules, advanced cloudy swelling, granules in the cytoplasm and irregularly staining nuclei. Goto<sup>11</sup> observed that acid (from 0.5 per cent hydrochloric acid to 1 cc per kilogram) administered by mouth to two dogs produced an "acute nephritis."

Acid has been used in these experiments in relatively large quantities over a short period of time, and the effect has been similar to that produced by other more toxic chemicals. Acute tubular injury has resulted.

#### PLAN OF EXPERIMENTS

The experiments described in this paper were planned to determine whether a mild chronic acidosis, or a lowering of the plasma carbon dioxide capacity, extending over a long period of time, would result in kidney damage.

The acidosis was produced by administering by stomach tube one-tenth normal hydrochloric acid or one of the hydrochloric acid forming substances, ammonium chloride or calcium chloride, to rabbits and dogs. The dosage of acid-forming substances was so regulated that the carbon dioxide capacity of the plasma became and remained slightly below normal over periods of months. It was difficult to regulate this dosage for rabbits. They often contracted a severe acidosis. Specimens of urine were examined at regular intervals for albumin, the  $p_H$  was determined and the sediment was examined microscopically.

#### ACIDOSIS IN RABBITS, MATERIAL AND METHODS

Fifteen young animals weighing approximately 2 Kg were used. Six of these were kept as controls. All animals were maintained under the same living conditions, on a diet of oats and various greens and water as desired. For spontaneous ear infection with *B. necrophorus*, which made its appearance in a few animals, these animals were treated by pouring ether into the ear every other day until the infection disappeared completely.

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9 Ewing, James. Acidosis and Associated Conditions, *Arch Int Med* 2: 330 (Nov.) 1908.

10 MacNider, W. deB. Studies Concerning the Influence of a Disturbance in the Acid-Base Equilibrium of the Blood on Renal Function and Pathology. Study I. The Effect of Acid and Alkaline Solutions on Renal Function and Pathology in Normal Dogs, *J Metabolic Research* 3: 511 (April) 1923.

11 Goto, Kingo. A Study of Acidosis, Blood Urea and Plasma Chlorides in Uranium Nephritis in the Dog, and of the Protective Action of Sodium Bicarbonate, *J Exper Med* 25: 693 (May) 1917.

Weekly examinations of the urine were made on urine freshly obtained by pressure on the bladder. In order to make certain that the bladder should contain a sufficient volume of urine, the animals were put into rat cages for three or four hours previous to taking the specimen of urine. They were sufficiently crowded and uncomfortable in these small cages so that they did not urinate during that period. The  $p_H$  of the urine was determined colorimetrically with the LaMotte standards on all specimens of urine acid to litmus. Albumin was determined by heat and acetic acid. Acid was also added to urine which was cold, as it was found that frequently a precipitate formed under these conditions. Albumin as reported refers to the density of the cloud in the heated specimen after that in the cold urine has been subtracted. It is reported as a faint trace, trace, one plus, two plus or three plus. Microscopic examination of the sediment obtained by centrifugalization was made promptly.

Blood for plasma carbon dioxide capacity was drawn at weekly or bi-weekly intervals as the condition of the animal warranted. The specimen was collected by inducing hyperemia in the ear with ether, cutting the marginal vein and allowing the blood to fall into an oxyalated tube. After gently mixing with a rod, oil was poured on the surface, and the blood was centrifugalized. This is not an accurate way of collecting blood for gas analysis. The method was checked, however, by drawing simultaneous specimens from the heart. The difference of about 3 per cent by volume was of no practical importance in these experiments. A rabbit's plasma carbon dioxide capacity has normal limits as wide as 45-70 per cent by volume. The method of analyzing the blood was that described by Van Slyke<sup>12</sup>. The analyses of the last six months were made on the constant volume Van Slyke machine<sup>13</sup>.

Nine of the rabbits received tenth normal hydrochloric acid, calcium chloride or ammonium chloride by stomach tube over periods of time which varied from ten days to one year. The time and dosage, together with urine, blood and post-mortem observations, are given in tables 1 and 2.

The use of tenth normal hydrochloric acid as a means of lowering the reserve alkali of the blood needs no explanation. Ammonium chloride and calcium chloride increase the chloride anions of the blood, because in the case of ammonium chloride, the ammonia is probably converted into neutral urea, while in the case of calcium chloride, a large portion at least of the calcium is eliminated in the stool, while the chlorine ion is absorbed. Either substance, therefore, increases the hydrochloric acid metabolism of the body. Haldane<sup>14</sup> has reported the production of acidosis in himself both after the ingestion of calcium chloride and ammonium chloride. Gambler, Ross, and Tisdall<sup>15</sup> and Gamble and Ross<sup>16</sup> administered calcium chloride, ammonium chloride, and hydrochloric acid in the treatment of tetany and proved that calcium chloride

12 Van Slyke, D. D. Studies in Acidosis. II. A Method for the Determination of Carbon Dioxide and Carbonates in Solution, *J Biol Chem* **30** 347, 1917.

13 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523 (Sept.) 1924.

14 Haldane, J. B. S., Hill, R., and Luck, J. M. Calcium Chloride Acidosis, *J Physiol* **57** 301 (June) 1923. Haldane, Priestley, Baird and Douglas. Ammonium Chloride Acidosis, *J Physiol Proceedings* **57** 11 (Feb.) 1923. Haldane, J. B. S. Experimental and Therapeutic Alteration of Human Tissue Alkalinity, *Lancet* **1** 537 (March 15) 1924.

15 Gamble, J. L., Ross, G. S., and Tisdall, F. F. Studies in Tetany. Effect of Calcium Chloride Ingestion on the Acid-Base Metabolism of Infants, *Am J Dis Child* **25** 445 (June) 1923.

16 Gamble, J. L., and Ross, G. S. Studies in Tetany. The Effect of Hydrochloric Acid Producing Substances on the Acid-Base Metabolism of an Infant, *Am J Dis Child* **25** 470 (June) 1923.

and ammonium chloride as well as hydrochloric acid lowered the plasma bicarbonate. Hydrochloric acid and presumably the other substance also lowered the  $p_H$  of the plasma. They found that only about 40 per cent of the calcium chloride ingested acts as hydrochloric acid, while probably all of the ammonium chloride ingested exerts an acid effect. One gram of ammonium chloride, which contains approximately 0.66 Gm chlorine, would be equivalent to 180 cc tenth normal hydrochloric acid. One gram of calcium chloride, if all the calcium were eliminated via the stool, and all the chlorine absorbed, would be equivalent to approximately the same, 180 cc tenth normal hydrochloric acid.

Because of the possibility that ammonium chloride administered over a long period of time might introduce extraneous effects caused by ammonia and not by acid, three of the rabbits received tenth normal hydrochloric acid over long intervals of time during the experiments. There was no difference in the results. Calcium chloride was given to the rabbits during a large part of the experimental period. Tenth normal hydrochloric acid was finally stopped because such large volumes of fluid were necessary. The ammonium chloride and calcium chloride were given in 2 per cent solution.

The animals, with the exceptions noted in the tables, were killed, and autopsy was performed immediately. Sections were fixed in Zenker's solution and were stained with hematoxylin and eosin stain or by Giemsa's method.

#### EXPERIMENTAL OBSERVATIONS ON RABBITS

The individual variations in dosage and in the response of the animal to the acid make it impracticable to average the figures and present the data in a single table. The animals will be described as a single group during the first few days. They will then be divided into two groups: animals that never had a severe acidosis, that is a plasma carbon dioxide combining power below 30 per cent by volume, and the animals that developed a severe acidosis. Tables 1 and 2 contain the data for these two groups.

Previous to giving the acid, the specimens of urine of the nine animals used in the experiment were alkaline, there were no casts in the sediment, and eight of the nine had no albumin. One showed a faint trace. The plasma carbon dioxide capacity varied between the limits of 46 per cent by volume and 70 per cent by volume. These observations were made over a control period of one month.

The administration of from 5 to 7 Gm of ammonium chloride to four animals over a period of three days to one week resulted in the appearance of albumin in the urine, which was a faint trace in one animal but a one plus amount in the others. The specimens of urine became acid, the  $p_H$  dropped as low as 5.4. Casts had appeared in the urine of one animal. After 7 Gm of calcium chloride given over the period of a week to one animal, the albumin test gave a plus two reaction. The administration of from 100 to 350 cc of tenth normal hydrochloric acid, given to four rabbits over a similar period of time, produced an acid urine, and in all but one case albumin varying from a faint trace to one plus. In all these animals the plasma carbon dioxide capacity was unchanged.

At the end of the first few days, without changing the reserve alkali of the body, the animals had been forced to excrete an acid urine and in all but one case varying amounts of albumin, while one rabbit had showed casts. It soon became evident, however, that the rabbit that does not produce ammonia to neutralize the acid eliminated in the course of

TABLE 1—*Severe Acidosis*

Rabbit	Duration of Experimental Period	Dosage of Drugs Administered	Urine Observations			Carbon Dioxide per Cent by Volume		Hours Post mortem Cause of Death	Microscopic Kidney Observations
			Average		Casts	Average	Lowest		
			pH	Albumin					
4	11 days	16.2 Gm $\text{NH}_4\text{Cl}$	6.4	+	Hyaline, granular	39	12	0 Killed	Epithelium of convoluted tubules swollen, vacuolated, completely filling lumen, nuclei showed karyolysis, slight spontaneous nephritis
7	18 days	18.6 Gm $\text{NH}_4\text{Cl}$ , 8.0 Gm $\text{NaHCO}_3$	4.9	++	Hyaline, granular	37 61*	20	0 Acidosis	No swelling of tubular epithelium, nuclei filled with many deep purple punctate dots of chromatin, numerous casts in tubules, no spontaneous nephritis
11	36 days	26.8 Gm $\text{NH}_4\text{Cl}$	5.2	+	All types terminally	45	15	Biopsy	Tubular epithelium swollen, vacuolated, both pyknosis and karyolysis of nuclei, slight spontaneous nephritis
	3 weeks		7.0	++	All types terminally	15		0 Killed	Tubular epithelium in places showed regeneration, many epithelial cells with no cytoplasm and pyknotic nuclei, pyknosis much more extensive, numerous casts in tubules
14	8.5 mo	5.510 cc N/10 $\text{HCl}$ , 45.0 Gm $\text{NH}_4\text{Cl}$	5.4	++	Granular, occasionally all types	50	11	Biopsy†	Some cellular debris and casts in tubules, slight spontaneous nephritis, essentially normal
	7.5 wk	22.0 Gm $\text{NH}_4\text{Cl}$	5.0	++	All types	47	14	0 Killed	Slight swelling of convoluted tubular epithelium, some nuclei of epithelial cells pyknotic, slight spontaneous nephritis
6	11 mo	166.0 Gm $\text{NH}_4\text{Cl}$	5.0	++	All types	35	18	Biopsy	Tubular epithelium swollen, vacuolated, many nuclei pyknotic, no spontaneous nephritis
	3 weeks							0 Killed	Condition practically unaltered, slightly improved

\* Per cent by volume of carbon dioxide at time of death

† No acidosis at time this kidney was removed

metabolism rapidly acquires a severe acidosis. Two of the animals were killed by the acidosis, one in eleven days and one in eighteen days, before this fact was fully appreciated. Even with careful watching subsequent animals were thrown into periods of severe acidosis from which they recovered.

The group of nine animals, therefore, is divided into two groups, one group consisting of rabbits 15, 16, 17 and 18, that at no time had a plasma carbon dioxide capacity below 30 per cent by volume. Animals 4, 6, 7, 11 and 14 had severe acidosis one or more times.

Table 1 summarizes the procedures and results in the group that had severe acidosis. Grossly and microscopically, the pathologic observations were uniform. The kidneys, grossly, were moderately swollen and pale. When spontaneous nephritis, so characteristic of rabbits, was present, it was recognized by small diffuse pits on the surface. On section, the proportion of cortex to medulla was normal. Extreme paleness was the outstanding feature.

Microscopically, with Giemsa's stain, the epithelium of the convoluted tubules was undergoing acute degeneration. The cells were so swollen as to fill the lumen completely, the cytoplasm was granular and vacuolated, the nuclei were usually deep violet, shrunken and irregular in contour, although rabbits 4 and 11, under treatment a short time, showed swollen, pale nuclei also. There were casts in the collecting tubules and a finely granular precipitate in some of the glomerular spaces. The glomeruli were normal. The observations were the same irrespective of the duration of the experiment. There was no intertubular proliferation of cells. Although the kidneys of these animals had been subjected to prolonged irritation, which was sufficient to cause the constant appearance of albumin and casts in the urine, no indication of a chronic response on the part of the tissues was obtained. The picture was that of a mild acute injury to the tubular epithelium and was essentially that of cloudy swelling.

Animals 4 and 7 are interesting in that they both received approximately the same amount of ammonium chloride and both were killed because they were in a moribund condition caused by acidosis. Rabbit 7, fig 2, however, had received 8 Gm of sodium bicarbonate during a period of two days previous to his death. His plasma carbon dioxide had returned to normal. With the exception of the great number of casts in the tubules and a slight degree of pyknosis of the nuclei, his kidneys were not microscopically abnormal, while those of rabbit 4, fig 1, showed the tubular degeneration described in the foregoing. The nuclei were swollen and pale, or pyknotic.

Rabbit 11 was operated on in the stage of severe acidosis, and a portion of the right kidney was removed. This showed microscopically the characteristic picture of tubular degeneration. The kidney became infected postoperatively. Leukocytes and bacteria appeared in the urine, and the animal was killed seven days after the operation. In addition to the local area of infection in the right kidney, an early thrombus was found microscopically on the mitral valve. Besides the tubular degeneration in the kidneys, there often were adhesions between the glomerular

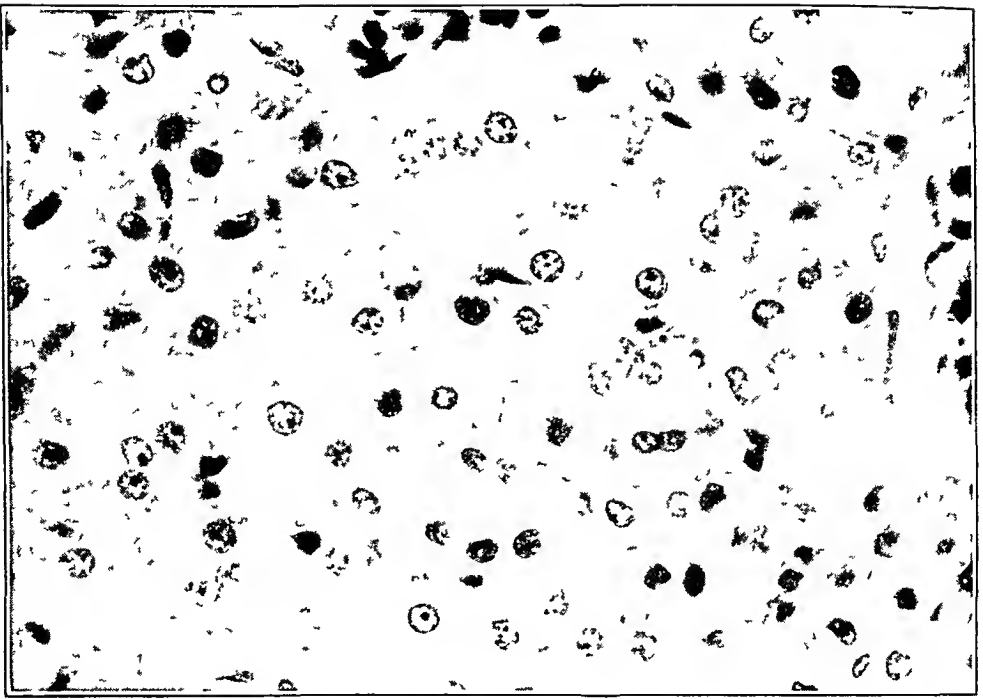


Fig 1—Convoluted tubules from the kidney of rabbit 4 The animal had received 162 Gm of ammonium chloride over a period of two days The plasma carbon dioxide had fallen to 12 per cent by volume The combination of swollen cytoplasm with nuclei which are either swollen and pale or pyknotic is characteristic of early acute acidosis

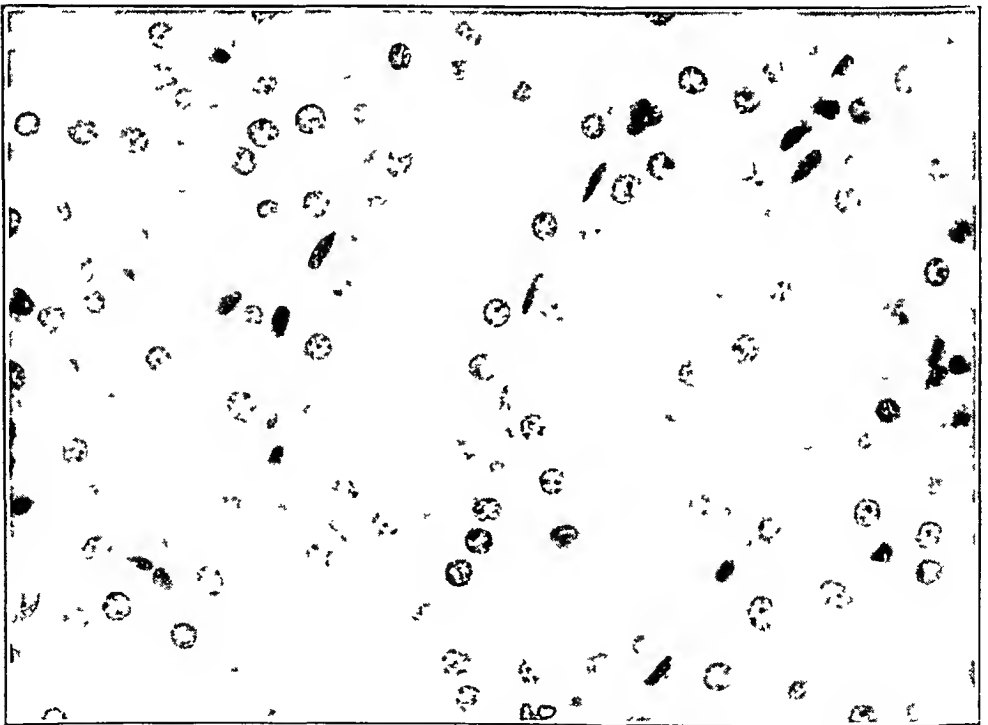


Fig 2—Convoluted tubules from the kidney of rabbit 7 The animal had received 186 Gm of ammonium chloride over a period of seventeen days The plasma carbon dioxide capacity was less than 20 per cent by volume two days before death, but due to the ingestion of sodium bicarbonate the plasma carbon dioxide had returned to 61 per cent by volume before death The tubules are relatively normal except for the increased chromatin in the nuclei

tuft and the capsule. In view of the negative observations in the glomeruli of the other animals, this must be attributed to the superimposed infection.

The left kidney was removed from rabbit 14 one month after the animal's plasma carbon dioxide had fallen to 10.7 per cent by volume. At this time the urine contained all types of casts in great numbers and a three plus albumin reaction. The blood urea nitrogen was 28 mg per hundred cubic centimeters of blood. By way of treatment the animal was given sodium chloride, 4 Gm daily by stomach tube, for two days. At the time of operation, one month later, the results of all tests were normal, except that there was a trace of albumin in the urine. Macroscopically and microscopically, the kidney removed for biopsy was normal with the exception of a few casts in some of the collecting tubules.

TABLE 2—*Mild Acidosis*

Rabbit	Duration of Experimental Period	Dosage of Drugs Administered	Urine Observations			Carbon Dioxide per Cent by Volume		Hours Post mortem Cause of Death	Microscopic Kidney Observations
			Average		Casts	Average	Lowest		
			pu	Alb					
17	24 days	650 cc N/10 HCl	5.6	+	Occasional hyaline and granular	59	59	? <17 Pneumonia	Postmortem swelling of tubular epithelium, serous precipitate in capsular space spontaneous nephritis
18	2 mo	1,850 cc N/10 HCl 6 Gm NH <sub>4</sub> Cl	6.0	++	Occasional hyaline and granular	61	58	<3	A few pyknotic nuclei in tubular epithelium, spontaneous nephritis
16	2½ mo	3,125 cc N/10 HCl	6.0	Trace	Hyaline terminally all types	56	34	0 Killed	Serous and cell debris in tubule, many pyknotic nuclei, slight spontaneous nephritis
15*	13 days	13 Gm CaCl <sub>2</sub>		+	0	57	55		Same as 16, also convoluted tubular epithelium swollen, no spontaneous nephritis
	7 mo	5,570 cc N/10 HCl, 42 Gm NH <sub>4</sub> Cl	5.5	++	All types in moderate numbers	56	30	<5	

\* There was an interval of six weeks between the two experimental periods.

During the following seven and a half weeks the animal received 22 Gm of the ammonium chloride. In the middle of this period a severe acidosis developed. The plasma carbon dioxide capacity was reduced to 13.7 per cent by volume. The animal recovered from this, however, and at the time it was killed, the plasma carbon dioxide capacity was 25 per cent by volume, the urine showed a plus one albumin reaction and a few of all types of casts. Grossly, the kidney was somewhat pale but otherwise normal and weighed just under 9 Gm. Microscopically, the changes already described were found but to a less marked degree. Only occasional pyknotic epithelial nuclei were found, and the cytoplasm was less granular, swollen and vacuolated. There were a few scars of spontaneous nephritis.

Rabbit 6 was operated on and his right kidney removed at a time when his plasma carbon dioxide capacity was 41 per cent by volume. The urine had a  $p_H$  of 5.1, albumin + + +, and showed hyaline and granular casts. There was severe bleeding at the time of the operation, the animal failed to gain weight afterward. He was finally killed three weeks later because of a stitch abscess which persisted and extended in spite of treatment. The abscess had involved the peritoneal wall at the site of the incision, and the intestines in the vicinity were matted together by dense adhesions. In spite of this secondary infection, the condition

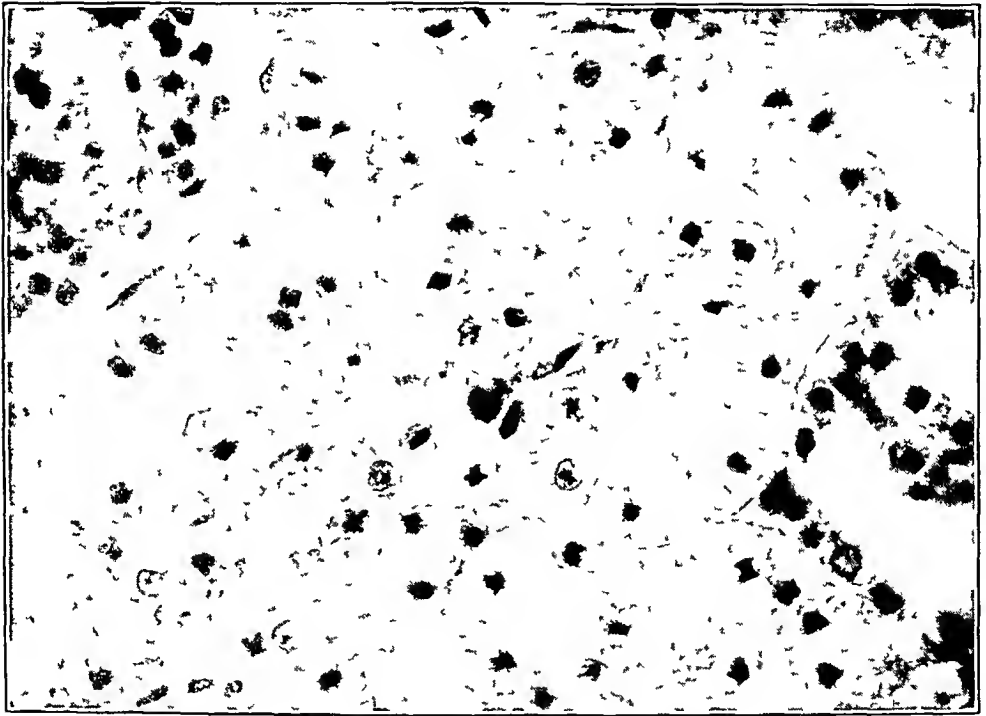


Fig 3—Convoluted tubules from the kidney of rabbit 6, removed at operation one year after the onset of acidosis. The plasma contained 41 per cent by volume of carbon dioxide. The marked pyknosis of the nuclei, with swelling and granulation of the cytoplasm is characteristic of protracted acidosis.

of the remaining left kidney, fig 3, was somewhat better than of that removed at biopsy. The epithelium was not so swollen, and the pyknosis of the nuclei had in part disappeared. The kidney removed at biopsy showed the changes already described.

Of the four animals, table 2, that at no time contracted a severe acidosis, three died unexpectedly and autopsy was not performed immediately. Rabbit 16, which was killed, therefore furnishes the best example of this group. The same changes in convoluted tubules but to a less marked extent, were found microscopically.

The six control animals lived in the laboratory for from one month to sixteen months. All but one were killed and autopsy immediately performed. The animals that were kept ten months and longer occasionally showed a trace of albumin and, in some instances, a plus albumin reaction in the urine. This was most often associated with the spontaneous development of an acid urine. Three of the animals had hyaline and finely granular casts at times. The albumin and casts persisted in the case of no. 9 who at autopsy showed extremely extensive spontaneous nephritis. All had at least a few pits in the surface of their kidneys which microscopically were due to localized areas where tubules were collapsed, accompanied by round cell infiltration and connective tissue proliferation.

#### GENERAL BODILY REACTION OF RABBITS

The weight curve went down whenever the animals acquired a severe acidosis or a moderate acidosis extending over a long period of time. At autopsy the body fat was much decreased.

Pathologic changes elsewhere than in the kidneys were conspicuously absent. The aorta was examined particularly with reference to the development of arterial lesions, but only the small plaques which represent spontaneous degeneration of the media were found.

Rabbit 6 had progressive softening of his teeth during the last two months of his life, so that when he died the lower front teeth were practically gone. Dr. P. R. Howe had two of the teeth analyzed for calcium and found them deficient. The bones of the skull were so thin that they could readily be cut with an ordinary scissors. After twenty-four hours in Zenker's solution, they could be sectioned with a microtome. The long bones did not show any gross thinning, but the ribs were extremely soft. Loss of calcium and of fat in experimental acidosis has already been reported by Goto.<sup>17</sup> The epithelium of the lungs of this animal, no. 6, was vacuolated as though undergoing hydropic degeneration.

When an animal has severe acidosis, his respirations become slow and deep. His head is retracted. He sits quietly unless disturbed, and when he attempts to walk, he falls toward one side. Later, he lies on one side and exhibits spasmodic twitching of the extremities.

#### CHRONIC ACIDOSIS IN DOGS

Seven female mongrel dogs were used for the experiment. They ran together on the roof of the building during the day and occupied separate pens at night. Their diet consisted of Spratt's Dog Biscuit and meat. They all had the mange and were treated with sulphur ointment. It persisted in only one, no. 3.

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<sup>17</sup> Goto, Kingo. Mineral Metabolism in Experimental Acidosis, *J. Biol. Chem.* **36**: 355 (Nov.) 1918.

Experimentally the dogs were treated in the same manner as the rabbits, except that the plasma carbon dioxide determinations were made much less frequently because the onset of acidosis in the dogs was more gradual

EXPERIMENTAL RESULTS

In table 3 are summarized the experimental procedures in the five animals who were given ammonium chloride, calcium chloride and tenth normal hydrochloric acid. About two weeks after the onset of treatment, the specimens of urine showed a faint trace of albumin. It was

TABLE 3—*Acidosis in Dogs*

Dog	Wt, Kg	Duration of Experimental Period	Dosage of Drugs Administered	Urine Observations			Carbon Dioxide per Cent by Volume		Hours Post mortem Cause of Death	Microscopic Kidney Observations
				Average		Casts	Average	Low est		
				pH	Albu min					
1	14	4 mo	56 Gm NH <sub>4</sub> Cl, 498 Gm CaCl <sub>2</sub>	6.0 Terminally 4.9	+	Hyaline, granular in moderate numbers	30	21	0 Killed	Convoluted tubular epithelium vacuolated nuclei showed karyolysis and occasional pyknosis casts in collecting tubules, spontaneous nephritis
2	17	5½ mo	26.590 cc N/10 HCl, 124 Gm NH <sub>4</sub> Cl, 519 Gm CaCl <sub>2</sub>	5.9	Trace	Hyaline casts in about one half the examinations	45	31		Animal showed leukocytes and bacteria in the urine and the experiment was stopped
3	15	5 mo	35.475 cc N/10 HCl, 196.5 Gm NH <sub>4</sub> Cl, 171.5 Gm CaCl <sub>2</sub>	5.9	Trace	A few hyaline	40	27		Urine free from albumin and casts six weeks after stopping acid
4	17	3½ mo	27.865 cc N/10 HCl, 202.5 Gm NH <sub>4</sub> Cl, 227.0 Gm CaCl <sub>2</sub>	6.0	Trace	Occasional hyaline and granular rare cellular	42	32		Urine clear of casts in two weeks, of albumin in four weeks after treatment
5	12	5 weeks	207 Gm CaCl <sub>2</sub>	5.9	Trace	Occasional hyaline				Urine returned to normal in two weeks

not until acidosis was well established, about 35 per cent by volume carbon dioxide, that casts appeared constantly and then only in small numbers. With the exception of dog 1, which was pressed to a point where it became necessary to kill her, the albumin test was never more than plus one. The urine pH did not vary between wider limits than 5.7 to 6.1 during the whole course of the experiment. Two dogs were starved for seven days but still maintained the same urine pH even when given 4 Gm calcium chloride by stomach tube.

Terminally, when dog 1 had a plasma carbon dioxide capacity of 21 per cent by volume, her urine pH fell to 4.9, she had a two plus albumin

reaction and all types of casts in considerable numbers. She was killed because she had lost weight and vomited every thing that she ate or drank.

The right kidney weighed 70 Gm, the left 75 Gm. This is above normal weight for a 14 Kg dog<sup>18</sup>. The capsule stripped readily, although the surface of the kidney was irregularly pitted. It presented the same picture as that of the spontaneous nephritis kidney in a rabbit. On section abnormalities were not noted grossly, with the exception of the infrequent fine white striations radiating in from the capsule and caused by the spontaneous lesions. All the other organs were also normal in appearance.

Microscopically, the convoluted tubules of the kidney were slightly swollen and showed extensive vacuolization suggesting hydropic degeneration. The nuclei were irregular in shape, usually larger than normal and pale. There were casts in the collecting tubules. There was no intertubular cellular proliferation. The picture as before was similar to that of cloudy swelling.

In addition to this change, which may be attributed to the acidosis, there were localized areas of spontaneous nephritis. These consisted in proliferation of the epithelium of the capsule with hyalinization and obliteration of the capsular space. This usually involved two or three contiguous glomeruli. The adjacent tubules were collapsed. An occasional small arteriole showed hyaline change. Goodpasture<sup>18</sup> described similar changes. MacNider<sup>19</sup> also describes spontaneous lesions in the dog's kidney. One animal that was killed as a control had smaller lesions of a less marked character in the glomerular tufts resembling those described by MacNider.

Of the other four animals, experimentation was stopped on no. 2 because she developed an infection of the urinary tract. The calcium chloride was stopped on the other dogs when the results from no. 1 were found to resemble those obtained on rabbits. The specimens of urine became free from casts and albumin in from two to six weeks.

In summary therefore, the effect of an acidosis on dogs' kidneys was similar to that on rabbits' kidneys. An acute degeneration of the epithelium of the convoluted tubules resembling cloudy swelling resulted, which did not produce any of the reaction normally associated with a chronic process. The main difference between the dogs and the rabbits was the extreme difficulty in forcing the dogs to form a more than normally acid urine.

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18 Goodpasture, E. W. Anatomical Study of Senescence in Dogs with Especial Reference to the Relation of Cellular Changes of Age to Tumors, *J. M. Research* **38** 127 (May) 1918.

19 MacNider, W. deB. A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, *J. M. Research* **34** 177 (May) 1916.

## COMMENT

Rabbits have been used extensively for work in experimental nephritis. Often much encouragement has been derived from the appearance in the urine of large quantities of albumin and numerous casts. Both are readily obtained in rabbits if the animal is forced to excrete an acid urine for a few days. Even when the irritation is carried over as long a period of time as a year, and the acidosis is forced to a point of almost lethal severity, with a resulting three plus albumin reaction and all types of casts, the injury proves microscopically to be only an acute tubular one resembling cloudy swelling. No permanent or chronic injury to the kidney is effected, and repair may take place rapidly and completely when the acidosis is stopped.

In carnivorous dogs the same transitory type of injury to the tubular epithelium accompanies an acidosis. The animal protects himself against the development of an acid urine efficiently, however, and the albumin and casts are slower to appear and small in quantity until a drop in the  $p_H$  of the urine occurs.

The experimental production of nephritis with uranium nitrate is accompanied by acidosis. The fact as reported by MacNider<sup>20</sup> and Goto<sup>21</sup> that the toxicity of uranium nitrate is diminished by sodium carbonate may well depend on the neutralization of acids which are causing destruction of tubular epithelium. The same condition probably accounts for the diminution of albumin and casts in certain human patients with nephritis following alkali therapy as reported by Hosslin<sup>4</sup> and others.

It is also interesting, in view of the use of calcium and ammonium chloride to relieve tetany and edema, that such large quantities may be given to animals over long periods of time, and that such a severe acidosis may be incurred apparently without any permanent injury.

Our results emphasize the importance that an acid urine may have in producing the clinical picture of an injured kidney. Post and Thomas<sup>21</sup> find that in a large majority of patients with orthostatic albuminuria, neutralization or alkalinization of the urine by administering alkaline salts or by regulating the diet prevents the development of the albumin and casts. We are at present trying to confirm this and to determine urine  $p_H$  in patients with orthostatic albuminuria.

Another circumstance under which albumin and casts occur in the urine of a person who does not have nephritis is following severe muscular exercise. At this time the urinary acidity is increased. Bornstein

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20 MacNider, W. deB. The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, *J. Exper. Med.* **23** 171 (Feb.) 1916.

21 Post, W. E., and Thomas, W. A. Orthostatic Albuminuria, *J. A. M. A.* **80** 293 (Feb. 3) 1923.

and Lippmann<sup>22</sup> report that giving sodium bicarbonate by mouth lessens or does away with the albumin and casts from this cause

#### SUMMARY

Calcium chloride and ammonium chloride both increase the acid metabolism when injected into the stomach of an animal

Rabbits were given varying doses of tenth normal hydrochloric acid and ammonium chloride over periods of time extending from eleven days to one year. The plasma carbon dioxide capacity was lowered, and the animals excreted an acid urine. Casts and albumin were obtained constantly throughout the experimental period. At autopsy, however, the only demonstrable pathologic change in the kidney was acute degeneration of the convoluted tubules, similar to cloudy swelling, but also accompanied by marked pyknosis of the nuclei in cases of longer duration. When acid-forming substance was stopped, the kidney promptly returned to normal.

The results with dogs were comparable except that a greater dose of chloride had to be given in order to produce an acidosis, and that there were less albumin and casts.

The possible causal relation of acidosis to orthostatic albuminuria following strenuous exercise is discussed.

I wish to thank Miss Lewis of the Peter Bent Brigham Hospital for the Bun determinations on rabbit 14. This was the only rabbit who showed any retention of blood urea nitrogen.

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22 Bornstein, A, and Lippmann, A. Weitere Beitrage zur nicht Nephritischen Albuminurie, *Ztschr f klin Med* 86:345, 1918

# HEMORRHAGIC FOCAL GASTRODUODENAL LESIONS

## PRELIMINARY REPORT OF THREE CASES \*

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At the present time a large number of histories are being reviewed of patients who came to the Mayo Clinic complaining of gastro-intestinal hemorrhage. In this study only benign gastroduodenal lesions are included. In most of the series of cases that came to operation ulcers, gastric, duodenal or gastrojejunal, were found. There was, however, a surprisingly large number of cases in which a definite ulceration was not demonstrable at the operating table. In some of these, there were gastric, duodenal or esophageal varices, in a few, there was evidence of marked hepatitis, in others, splenomegaly or cirrhosis of the liver, and in a certain number it was assumed that a blood dyscrasia was responsible for the hemorrhages. Again, in other instances, some pathologic conditions of the gallbladder or appendix were found, and it was assumed that the condition was probably one commonly termed "gall-bladder bleeding" or "appendiceal bleeding."

In some of these patients, as well as in others in whom there was no obvious cause for the hemorrhage, some unusual condition was found about the pylorus or in the duodenum. The operating surgeon discovered a number of dense adhesions about the pylorus, an edematous condition of the duodenum, stippling of the duodenum, and other conditions. In most patients the roentgenologic examination failed to show a deformity in the stomach or duodenum, and the chemical investigation of the stomach did not show anything unusual. In some, the concentration of acids was high, but this was not a consistent observation. The history of dyspepsia, although not characteristically that of ulcer, in the presence of hemorrhage led, in the majority of these cases, to a diagnosis of peptic ulcer, in many of them laparotomy was advised. If the history had not included the complicating factor of bleeding, the probability is that the operation would not have been advised.

The possible relationship of focal gastroduodenal lesions to this condition was investigated because in many of these cases there was a history of acute infections, such as tonsillitis, adenitis, or acutely swollen joints just prior to the onset of bleeding. In this connection the obser-

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vations of Boas,<sup>1</sup> Husemann,<sup>2</sup> MacCarty,<sup>3</sup> Judd,<sup>4</sup> Roeder<sup>5</sup> and Konjetzny<sup>6</sup> became of interest

Roeder investigated the question of duodenitis and inferred that it is a relatively frequent condition. According to his description of the acute condition, the organ is considerably reddened and generally surrounded by cobweb-like or plastic inflammatory, peritoneal adhesions. He believes that the chronic type is common, and describes characteristic cobweb-like peritoneal adhesions surrounding the first portion of the duodenum, attached at times to the liver and to the gallbladder. The walls of the duodenum feel thickened, and the peritoneal coat seems congested.

MacCarty, in discussing duodenitis, writes

There is cellular destruction, congestion, edema and migration of leucocytes. The condition is seen as localized and also diffuse lesions, when diffuse, the appearance of the organ at exploration is not readily confused with duodenal ulcer, but when it is localized, the external appearance of the serosa is indistinguishable from that seen in association with small ulcers.

Boas and, subsequently, Husemann and many German writers have described acute, shallow, submucous ulcers scattered over the surface of the stomach and duodenum. At times these are complicated by gross hemorrhage.

Judd describes a duodenitis type of ulcer. He distinguishes this from the usual type of ulcer by the absence of distinct and demonstrable crater formation. If the surface of the mucous membrane is examined closely, single or multiple pin-point ulcers may be found. Both the submucosa and the muscularis are usually infiltrated with round cells which may extend a little distance into the tissues of the wall of the duodenum. He mentions the occasional complication of hemorrhage. He believes, however, that the bleeding associated with this kind of duodenitis is slight.

Konjetzny considered the possible relationship between chronic gastritis and chronic ulcer. He studied large series of preparations of resected stomachs and subjected these to thorough anatomic analysis. He found evidence of diffuse or focal gastritis in practically all those cases in which gastric ulcer was demonstrated. He also found similar lesions in those cases in which a duodenal ulcer was demonstrated.

1 Boas, Ismar. *Diagnostik und Therapie der Magenkrankheiten nach dem heutigen Stande der Wissenschaft* bearbeitet, Leipzig, G. Thieme, 1890-1893.

2 Husemann, T. *Die Gastroenteritis-Epidemie von Christiania* (November, 1888), *Deutsche med. Wchnschr.* **15** 960, 1889.

3 MacCarty, W. C. *Excised Duodenal Ulcers. A Report of Four Hundred Twenty-Five Specimens*, *J. A. M. A.*, **83** 1894 (Dec. 13) 1924.

4 Judd, E. S. *Pathologic Conditions of the Duodenum*, *Journal-Lancet*, **41** 215, 1921.

5 Roeder, C. A. *Duodenitis*, *Nebraska M. J.* **9** 252, 1924.

6 Konjetzny, G. E. *Die chronische Gastritis des Ulcusmagens*, *Zentralbl. f. Chir.* **50** 1026, 1923.

The following cases are submitted because they present some interesting and unusual lesions about the pylorus, about the stoma and in the duodenum. In all of these cases, hemorrhage rather than dyspepsia was the prominent symptom.

#### REPORT OF CASES

CASE 1—A chemist, aged 34, came to the clinic complaining of hemorrhages from the stomach. For about twenty years he had had occasional spells of dyspepsia, characterized at times by heartburn and vomiting. With the exception of tonsillitis and pleurisy, there was no history of any previous disease of importance. His history was indefinite, but there was apparently some relief from his symptoms after the taking of soda. In 1915, he had had an acute attack of gastro-intestinal disturbance which was diagnosed as ptomaine poisoning. The stools were dark, and he vomited small amounts of a black gastric content, which he believed contained altered blood. Four years later, he again suffered from pain in the epigastrium with vomiting, there was occasional diarrhea, and the stools sometimes contained blood. For about a week following this attack he experienced slight epigastric pain. Six months later, he had a similar experience. He again vomited blood and noticed tarry stools. He felt slight pain in the back, and on two or three occasions he lost consciousness. At that time he did not complain of any definite epigastric distress. In 1921, six years after the onset of the symptoms, he began to lose weight, and he occasionally felt slight supra-umbilical pain which usually reached its maximal intensity three or four hours after meals. At rare intervals he experienced rather acute transitory colicky pain in the epigastrium, which food and soda relieved temporarily. Between 1921 and 1925, he had had periodic spells similar to this. Two months before admission, several days after one of these attacks, during the course of which he felt extremely weak, he vomited blood and passed some tarry stools. Since that time, he had experienced almost constant, although slight, epigastric distress.

He was a slightly pale, thin man who had lost considerable weight. The heart and lungs were normal. The abdomen, with the exception of slight tenderness over the entire hypogastrium, did not reveal anything abnormal. The blood pressure was normal. The hemoglobin was 78 per cent, and the erythrocytes numbered 4,400,000. A complete differential count revealed nothing of significance. Platelets numbered 168,000. The calcium time, coagulation time and bleeding time were within normal limits. Careful investigation did not reveal any evidence of blood dyscrasia. Repeated roentgenologic study of the stomach and duodenum failed to show any evidence of a deformity. Roentgenograms of the chest and colon were also negative. Gastric acidity gave titration values of 70 for total acid and 54 for free hydrochloric acid, 150 cc of contents was withdrawn. Because of the history of dyspepsia complicated by hemorrhage, an operation was advised. Exploration revealed a small hemorrhagic spot on the anterior surface of the duodenum. The surgeon, however, was not certain that there was an ulcer. He said that there was considerable stippling about the duodenum, and suggested that it looked like duodenitis. The appendix was chronically inflamed and was removed. The cap of the duodenum was excised, and gastroduodenostomy was performed.

Prior to the operation, roentgenograms of the teeth had not been taken because the patient wore upper and lower plates. Since no other foci could be demonstrated as potential etiologic factors, it was decided to make a roentgen-ray examination of the alveolar processes, a few root tips were found. These were removed aseptically, and cultures were made. Three animals were injected intravenously with these emulsions, and in all cases they manifested duodenitis within twenty-four hours. There was an interesting similarity between the general characteristics of these lesions and those demonstrated in the duodenum at operation (fig 1).

CASE 2—A man, aged 25, gave a history of pneumonia earlier in life and of repeated attacks of tonsillitis. He began to have stomach trouble at about the age of 12. During the succeeding six years, he had had periodic attacks of distress in the epigastrium. The description of them was rather vague. However, he remembered having had heartburn, especially several hours after meals. Ever since he was 18, the dyspepsia had been more noticeable. He had experienced pain several hours after meals and had felt better after he had taken soda or a small amount of food. Occasionally he suffered severe pain in the epigastrium, and the pain passed through to his back. In 1921, when he was 21, his physician decided that the symptoms might be caused by appendicitis. Appendectomy was performed, but the symptoms continued as before. About eight months after the operation, he suddenly felt a severe pain in the epigastrium and went into a state of collapse. An emergency operation was performed, and a perforating ulcer was found. A purse-string was made about the ulcer, and gastro-enterostomy was performed. Shortly after this, he experienced

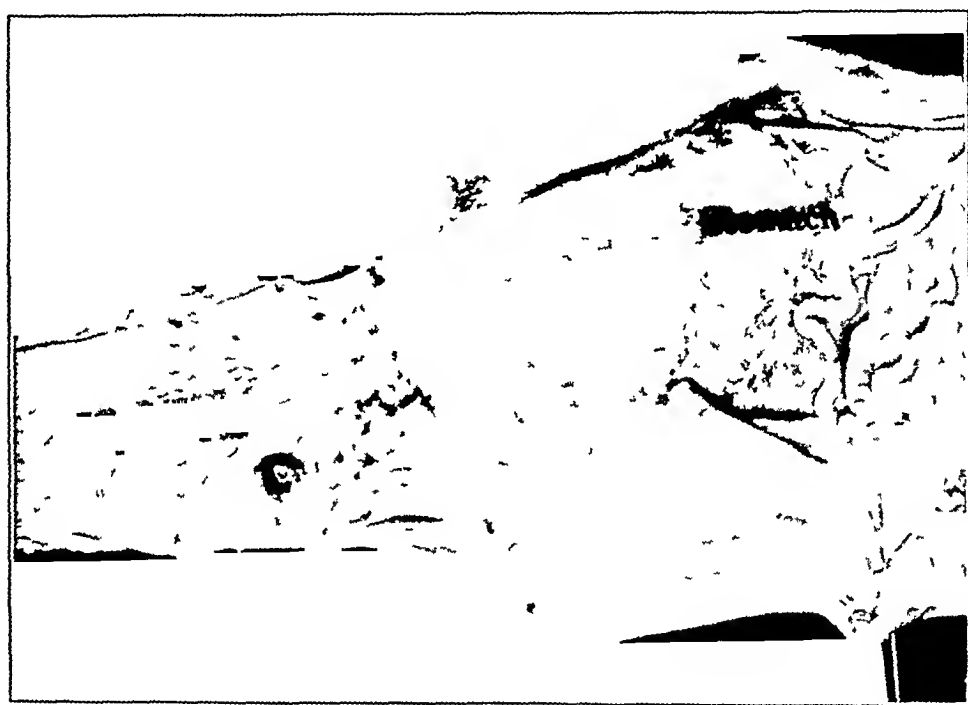


Fig 1—Specimen showing submucous hemorrhages in duodenum of animal twenty-four hours after intravenous injection of cultures obtained from extracted dental root in case 1

symptoms similar to those manifested prior to the operation. The pain now began in the epigastrium and radiated downward. It had the same relationship to meals as the former distress. On one occasion before coming to the clinic he vomited some blood, and for several days following this the stools were tarry. After this episode, he was weak for some time.

He was a tall, thin, undernourished, nervous young man with a systolic blood pressure of 86 and a diastolic blood pressure of 50. The tonsils had been excised elsewhere. There was some evidence of infection about the root of one tooth. Titration of gastric acids showed values of 76 for total acids and 36 for free hydrochloric acid. There was no evidence of recent bleeding or retention. The roentgenologic examination revealed a deformed duodenum and a free and apparently normal gastro-enteric anastomosis. Because of the similarity of the symptoms to those before gastro-enterostomy, because of the lower reference of the pain and because of the high acidity and a history of bleeding, a diagnosis of secondary peptic ulcer, probably gastrojejunal, was made, and an operation was

advised. The stomach was adherent to the liver and was freed. There was a suggestive scar on the anterior wall of the duodenum, which was not definitely an ulcer. The gastro-enteric anastomosis was then disconnected and turned from left to right. The ring of the stoma when excised showed a number of highly injected areas which the operating surgeon believed were responsible for the hemorrhages. Convalescence was uneventful. Several weeks after the operation, the tooth which had been infected periapically was extracted aseptically. Cultures prepared from this were injected into animals. Indurated areas with stippling and submucous hemorrhages in the duodenum were promptly produced in the animals on which the experiment was performed. These lesions were similar to the injected areas found about the stoma in the patient. My co-workers and I felt justified in assuming that the hemorrhages in this case were caused by gastrojejunitis.

CASE 3—A man, aged 58, came to the clinic complaining of gastric hemorrhages. There had been no other illness, with the exception of pleurisy and



Fig 2—Specimen showing rabbit's stomach with multiple small hemorrhagic ulcers following the intravenous injection of cultures from an extracted tooth in a patient with hemorrhagic duodenitis

several attacks of tonsillitis. For the last twenty-seven years he had had periodic spells of stomach trouble, with a gnawing sensation in the right upper abdominal quadrant. This distress would reach its maximal intensity several hours after meals. During the first of these attacks, he had vomited some blood and also had noticed tarry stools. These periodic spells of distress continued with only slight severity until 1906, eight years after the onset of symptoms, when he suffered a second hemorrhage. A third hemorrhage occurred six years after the second. After this complication, he felt well for fifteen years. Four weeks before his arrival at the clinic, there was another hemorrhage, which was followed in a week by further hematemesis. After the last attack he had occasional twinges of pain in the upper right abdominal quadrant, which were associated with slight flatulence and backache.

He was a pale, elderly man, but appeared to be well nourished. He had lost 16 pounds (7.3 Kg) during the last month. The tonsils and teeth were infected. Abdominal palpation failed to reveal any masses. There was slight tenderness in the upper right abdominal quadrant. Careful investigation for possible blood dyscrasia was negative. Titration of gastric acidity showed total acidity 40 and

free hydrochloric acid 18, 125 cc of gastric content was obtained. The first roentgenogram of the stomach was negative. The second showed a duodenal deformity which was assumed to be caused by ulcer. An operation was advised. The stomach and duodenum were normal. The gallbladder was slightly larger than normal, and there were some adhesions between it and the duodenum. The appendix contained a number of fecal stones and was chronically infected. The surgeon assumed that the appendix may have been the cause of the symptoms, including the hemorrhages, and he removed it. Convalescence was normal. Two teeth with periapical abscesses were extracted. Cultures were made and injected into animals. The resultant lesion in the rabbit involved the pyloric



Fig 3—Section of stomach and duodenum of rabbit showing extensive submucosal hemorrhages. These followed injection of culture obtained from the extracted teeth in a patient with hemorrhagic duodenal ulcer.

end of the stomach. A large submucous blood clot was found in the region of the pylorus and small hemorrhagic areas in the duodenum. This led to the assumption that the hemorrhages were probably caused by infectious gastritis and duodenitis, which at the time of the operation had disappeared and had left only multiple adhesions about the duodenum (figs 2 and 3).

#### COMMENT

These histories and case reports are typical illustrations of one group of patients in whom infectious lesions are probably responsible for gastro-enteric hemorrhages. They are additionally interesting and important because they stimulate speculation as possible forerunners of

chronic ulcer This condition occurs frequently Experimental work is being done to determine the specificity of certain strains of streptococci in the production of these lesions Recently a number of these patients came under my observation When an operation was performed shortly after the occurrence of hemorrhage, acute lesions were demonstrable in the potential areas of peptic ulcer, when the operation was postponed, and later advised mainly because of the history of hemorrhage, little was found to account for the bleeding In these patients all possible sources of focal infection have recently been removed, and a bland diet of high caloric content has been advised Thus far the results of these measures have been extremely encouraging It is, of course, too early to attempt to draw definite conclusions from the data which are obtainable at the present time It is my opinion, however, that many of these cases of so-called "appendiceal bleeding" or "gallbladder bleeding" are probably caused by acute lesions in the stomach or about or in the duodenum These lesions are known to heal promptly by the institution of the usual methods of treatment which promote healing and by the removal of all deterrent factors

# HODGKIN'S DISEASE

WITH PREDOMINANT LOCALIZATION IN THE NERVOUS SYSTEM,  
EARLY DIAGNOSIS AND RADIOTHERAPY \*

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Nearly a century ago, Hodgkin<sup>1</sup> first described the disease that now bears his name. In his original series of cases—of which five at most were authentic—there was involvement of (a) the lymph nodes in all cases, (b) the spleen in four cases, (c) the tonsils and the lymphoid tissues of the base of the tongue and pharynx in one case, and (d) the testicle possibly in one case.

In 1859 Wilks<sup>2</sup> reported one case of Hodgkin's disease in which he noted, in addition, invasion of the liver and kidneys. Six years later,<sup>3</sup> he published further observations showing the specific lesions also in the lungs.

In 1865, Cornil and Ranvier,<sup>4</sup> from a study of the literature and their own cases, had noted that Hodgkin's disease was more than a mere "affection of the absorbent glands and spleen." In addition to involvement of the lymph nodes and spleen, they found the specific lesions in the following organs and tissues: the skin, intermuscular tissues, subcutaneous tissues, bones, thymus, lungs, stomach and intestines.

Simultaneously with the publication of these articles in England and France, similar studies appeared in Germany, chief among which were those of Billroth,<sup>5</sup> Wunderlich,<sup>6</sup> Virchow<sup>7</sup> and Cohnheim.<sup>8</sup> It was the great merit of Cohnheim to perceive the generalized nature of Hodgkin's disease and its close similarity to leukemia in its widespread systemic dissemination. The new winged word, pseudoleukemia, coined by

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1 Hodgkin, T. On Some Morbid Appearance of the Absorbent Glands and Spleen, *Tr Med Chir Soc*, London **17** 68, 1832.

2 Wilks, S. Enlargement of Lymphatic Glands with Deposit in Spleen and Other Organs, *Tr Path Soc*, London **11** 257, 1859-1860.

3 Wilks, S. Cases of Enlargement of the Lymphatic Glands and Spleen (or Hodgkin's Disease), *Guy's Hosp Rep* **11** 56, 1865.

4 Cornil, A. V., and Ranvier, L. A. *Man d'Histologie Pathologique*, Paris 1869, p. 251.

5 Billroth, C. *Beitr z path Histologie*, 1858, pp. 168-171.

6 Wunderlich, C. A. Zwei Falle von Progressiven Multiplen Lymphdrusen Hypertrophien, *Arch f Phys Heilk* **2** 123, 1858, Pseudoleukämie, *Arch d Heilk*, Leipzig **7** 531, 1866.

7 Virchow, R. *Die Krankhaften Geschwulste*, 1864-1865, vol. 2, pp. 728-739.

8 Cohnheim, J. Ein Fall von Pseudoleukämie, *Virchow's Arch* **33** 451, 1865.

Cohnheim, may have been inappropriate and confusing to characterize the microscopic changes of Hodgkin's disease, as stated by Virchow and others.<sup>9</sup> The immediate popularity, however, of pseudoleukemia as a clinical concept and synonym for Hodgkin's disease and its almost universal adoption by the medical world for a great many years attests the historically and philosophically significant fact that Cohnheim's generalization of the systemic nature of Hodgkin's disease, based on the study of a single case, had struck a responsive cord in the minds of all students of this disease.

With medical attention now fully interested in this malignant malady of obscure etiology, numerous case reports began to appear in the literature in which ever wider areas of invasion were recorded until the protean and systemic aspects of Hodgkin's disease were fully established. And thus, in 1879, Gowers,<sup>10</sup> in his comprehensive contribution on Hodgkin's disease, gave details concerning the lesions not only in the lymph nodes and spleen, but also in the skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestine, large intestine, liver, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries.

The protean aspects of Hodgkin's disease thus stressed by Gowers received further corroboration and addition by a host of investigators, among whom were Birch-Hirschfeld,<sup>11</sup> Osler,<sup>12</sup> Ehrlich,<sup>13</sup> Murray,<sup>14</sup> Longcope,<sup>15</sup> Ziegler,<sup>16</sup> Ewing,<sup>17</sup> Symmers,<sup>18</sup> Sternberg<sup>19</sup> and others. As a result of their investigations, it was repeatedly and conclusively proved that not a single organ or tissue had escaped invasion in Hodgkin's disease.

Simultaneously with the recognition of the widely disseminated and protean character of Hodgkin's disease, repeated and numerous obser-

9 Hutchinson, R. Hodgkin's Disease, *Lancet* **1** 1404, 1904.

10 Gowers, W. R., in Reynold. *System of Medicine*, Philadelphia, 1879, vol 5, p 306.

11 Birch-Hirschfeld, in von Ziemssen. *Cyclopedia of the Practice of Medicine*, 1877, vol 16, p 829.

12 Osler, W., in Pepper. *System of Medicine*, Philadelphia, 1885, vol 3, p 921.

13 Ehrlich, P., in Nothnagel. *Specielle Pathologie und Therapie*, 1898, vol 8, p 81.

14 Murray, G. R., in Allbutt and Rolleston. *System of Medicine*, 1908 vol 4, p 459.

15 Longcope, W. T. *Oxford Medicine*, 1921, vol 4, p 1.

16 Ziegler, K. *Die Hodgkinische Krankheit*, Jena, 1911.

17 Ewing, J. *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922.

18 Symmers, D. The Clinical Significance of the Pathological Changes in Hodgkin's Disease, *Am J M Sc* **167** 157 (Feb) 1924, **167** 313 (March) 1924.

19 Sternberg, C. Lymphogranulomatosis, *Klin Wchnschr* **4** 529 (March) 1925.

vations had revealed its marked variation not only in the duration, character and acuteness of its clinical course, but also in its elective localization in different regions, tissues and organs in different persons. Although it is unquestionably true that in large series of cases the superficial lymph nodes are the first to attract clinical attention, numerous case reports have appeared in the literature in which the primary and predominant clinical localization occurred in the skin,<sup>20</sup> bones,<sup>21</sup> lachrymal and salivary glands,<sup>22</sup> nose,<sup>23</sup> tonsils,<sup>24</sup> trachea and bronchi,<sup>25</sup> esophagus,<sup>26</sup> stomach,<sup>27</sup> intestines,<sup>28</sup> liver,<sup>18</sup> spleen,<sup>18</sup> pancreas,<sup>29</sup>

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abdominal lymph nodes,<sup>30</sup> thymus,<sup>31</sup> mediastinum,<sup>32</sup> heart,<sup>33</sup> hemopoietic system<sup>34</sup> and nervous system<sup>35</sup>

The invasion of the nervous system in Hodgkin's disease first reported by Murchison<sup>30</sup> has since been noted by many observers, among whom were Goodhart,<sup>36</sup> Gowers,<sup>10</sup> Osler,<sup>12</sup> Welch,<sup>37</sup> Ziegler,<sup>16</sup> Longcope,<sup>15</sup> Askanazy,<sup>38</sup> Dietrich,<sup>39</sup> Schmorl,<sup>40</sup> Sternberg,<sup>19</sup> Hecker and Fischer,<sup>41</sup> Weber,<sup>42</sup> Holmes,<sup>43</sup> Pancoast,<sup>44</sup> Saalfeld<sup>45</sup> and others

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37 Welch, W H (footnote 35)

38 Askanazy, M (footnote 21)

39 Dietrich (footnote 21)

40 Schmorl (footnote 21)

41 Hecker and Fischer (footnote 35)

42 Weber (footnote 35)

43 Holmes (footnote 21)

44 Pancoast (footnote 35)

45 Saalfeld, C (footnote 19)

It is true that in the majority of instances the invasion of the nervous system was overshadowed by the extensive pathologic changes in the lymph nodes and viscera. That occasionally, however, the clinical course may be dominated almost entirely by the attack on the nervous system, is attested by the cases of Goodhart,<sup>36</sup> Askanazy,<sup>38</sup> Hecker and Fischer<sup>41</sup> and Walthard.<sup>46</sup>

However, in spite of the foregoing reports, the impression is still widely prevalent among physicians that the nervous system is so rarely involved in Hodgkin's disease as to be ignored in the differential diagnosis of diseases of the nervous system. Not only did I fail to see Hodgkin's disease mentioned in the standard textbooks on diseases of the nervous system, but even in the excellent recent monograph of Elsberg<sup>47</sup> on "Tumors of the Spinal Cord," the condition is ignored completely.

It, therefore, will be of considerable interest to report a series of ten of thirty-six patients with Hodgkin's disease observed at Montefiore Hospital during the years from 1914 to 1925, in which definite invasion of the nervous system was a striking clinical phenomenon. Some of these cases, which were of unusual clinical interest, will be reported in detail, while those of lesser value will be but briefly described.

#### REPORT OF CASES

CASE 1—*History*—N. S., a man, aged 47, was admitted to the neurological service of Montefiore Hospital, Aug 16, 1923, with a diagnosis of possible cord tumor. In May, 1921, the patient suddenly developed intense itching over the dorsal surface of his left forearm. There was not any visible eruption over the site of irritation. A few weeks later, a similar condition developed over the left upper outer thigh and scrotum. The itching was most intense at night, interfering with sleep. For two years the pruriginous condition continued unabated and was relieved only occasionally by local medication. In the meanwhile other symptoms appeared. In May, 1922, one year after the onset of the pruritus, the patient commenced to develop asthenia, fatigability and dyspnea on slight exertion. These symptoms grew slowly but progressively worse until May, 1923, when he was suddenly seized with severe cramplike, nonradiating pain in the upper part of the abdomen. He immediately consulted a physician, who diagnosed his condition as gastric ulcer. A roentgenologic study of the entire gastro-intestinal tract failed, however, to reveal any lesion. The abdominal pain kept recurring, and two or three weeks after onset, it began to radiate posteriorly to the dorsal spine. The colicky character gradually changed to a sharp, cutting and stabbing pain which radiated from the lower dorsal spine peripherally to the abdomen and down both lower extremities to the toes.

In June, 1923, the patient was admitted to a prominent hospital in New York where, after several weeks of observation and a most exhaustive study, including roentgen-ray examination and serologic tests, a diagnosis of spondylitis was made. The patient's condition gradually grew worse. In July, 1923, he began to develop symptoms of paraplegia and became bedridden. On Aug 8, 1923, he was admitted to the neurologic service of Montefiore Hospital.

<sup>46</sup> Walthard K. M. (footnote 35)

<sup>47</sup> Elsberg, C. Tumors of the Spinal Cord, New York, Paul B. Hoeber, 1924.

*Examination*—The patient was moderately pale but well nourished in the trunk and upper extremities. His chest, lungs and heart were normal. On abdominal palpation, he revealed an enlargement of the spleen to 1 inch below the costal margin and a moderate enlargement of the liver.

Neurologically, he revealed an almost complete motor paralysis and a loss of sensation in both lower extremities with sphincteric involvement. There was atrophy of the muscles of the thighs and legs. Hyperesthesia and hypalgesia were present from below up to the sixth and seventh dorsal segments.

Roentgen-ray studies of the skull, spine, chest and gastro-intestinal tract failed to elicit any gross lesions. The blood and spinal Wassermann tests were negative. The spinal fluid showed a slight increase in pressure but did not present other abnormalities. A study of the blood chemistry and a colloidal gold test failed to reveal any abnormality. A blood count showed red blood cells, 3,600,000, hemoglobin, 75 per cent, white blood cells, 11,600, polymorphonuclears, 55 per cent, small lymphocytes, 15 per cent, large lymphocytes, 28 per cent, eosinophils, 0.5 per cent, myelocytes, 1.5 per cent.

*Treatment and Course*—After four weeks of observation, study and consultation with the heads of several departments, the consensus of opinion, with one exception, was in favor of a spinal cord neoplasm and operative intervention.

On Sept. 19, 1923, a laminectomy revealed an extradural tumor, 8 cm. in length, lying between the third and the seventh dorsal vertebrae. Its upper and lower poles were defined sharply. Its surface was smooth and glistening. The laminae overlying the tumor were intact with the exception of those of the sixth dorsal, which were eroded. The lateral limits of the tumor were ill defined, the neoplasm apparently extending circumferentially all around the cord. The thickened portion of the tumor measured about 2 cm. The dura and cord were compressed but not invaded by the neoplasm. However, only an incomplete removal of the tumor was possible which on pathologic examination was reported as a sarco-endothelioma (fig. 1).

The patient made an uneventful recovery, and a few days after the operation was able to move his lower extremities actively in bed. The sphincteric involvement, however, continued and radiotherapy was decided on.

On Jan. 20, 1924, the patient received his first radium application in the form of a pack over the dorsal spine at the site of the operation. This was repeated about once a week, in fractionated doses until Aug. 23, 1924. There was moderate improvement in the paraplegic symptoms until July, 1924, when he began to have remittent fever up to 102° F. He also developed generalized enlargement of the lymph nodes and spleen.

A biopsy of the enlarged inguinal lymph nodes showed pathologic changes similar to those of the extradural neoplasm (fig. 2). Both specimens were submitted to Dr. James Ewing, whose diagnosis was Hodgkin's disease.

The patient grew progressively worse, and died with symptoms of generalization and severe secondary anemia. Autopsy was not permitted.

*Comment*—Among the many features of clinical interest presented by this case, the diagnostic are the most instructive. For one year persistent pruritus was the only symptom present before the advent of constitutional symptoms—asthenia, fatigability and dyspnea on exertion. At the end of two years after onset, the initial symptoms or paraplegia appeared, simulating the symptoms in a gastric ulcer. The paraplegia was believed to be caused by a tumor of the cord, this belief was verified on the operating table. There was not any suggestion of Hodgkin's disease even after the pathologist's first diagnosis of sarco-endothelioma. Only when generalized lymphadenopathy devel-

oped was Hodgkin's disease suspected, and biopsy showed that this condition was present

Why did this delay in diagnosis occur in a case which presented the highly suggestive clinical symptomatology of Hodgkin's disease with paraplegia, which has been described in the literature by Goodhart,<sup>36</sup> Oslei,<sup>12</sup> Longcope,<sup>15</sup> Parkes-Weber,<sup>12</sup> Steinberg,<sup>19</sup> Askanazy<sup>8</sup> and others?

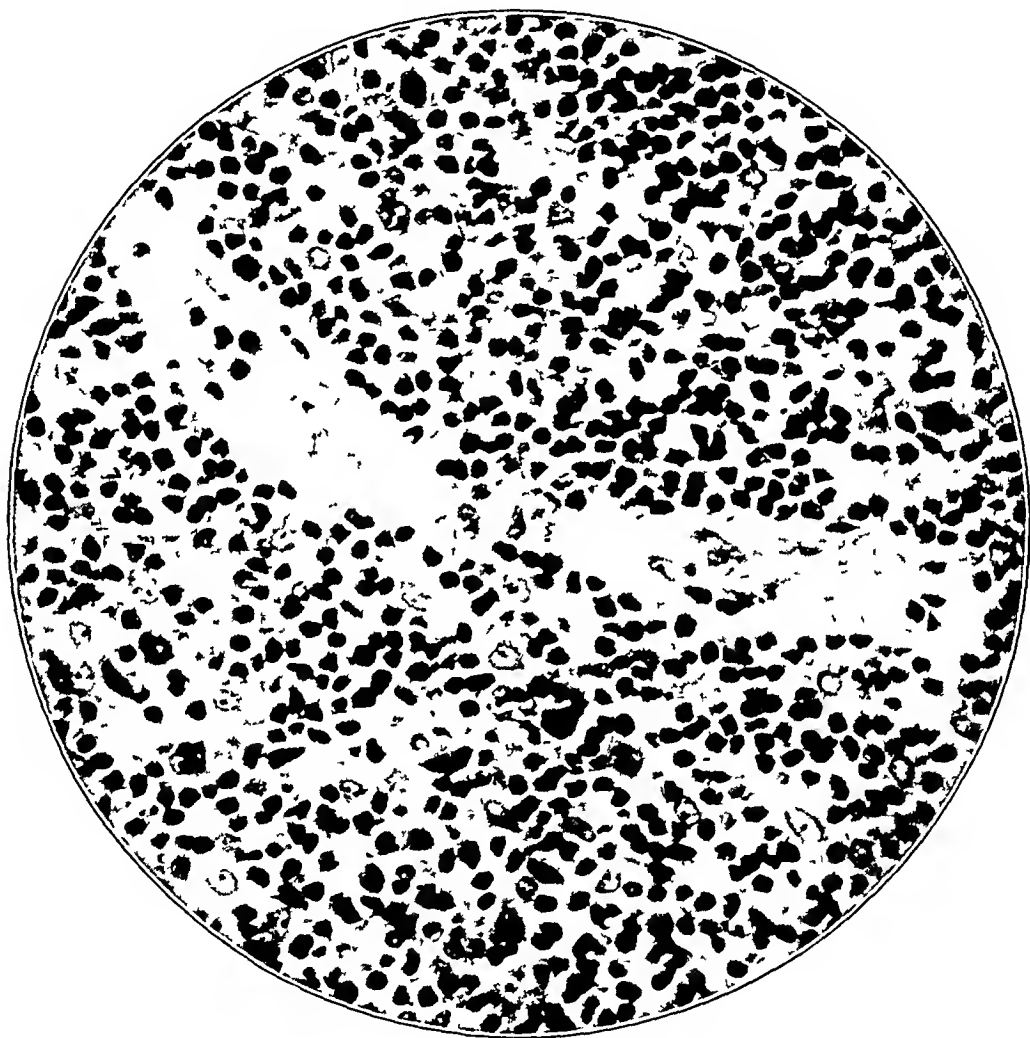


Fig 1 (case 1) —Spinal cord neoplasm showing hyperplastic cellular stage of Hodgkin's disease

The answer to this question involves the consideration and solution of two most important problems one local and the other general

The local problem involves the widely prevalent, erroneous, antiquated view that Hodgkin's disease is pathologically as well as clinically "an affection of the absorbent glands and spleen," with occasional deposits in other viscera. The abundant evidence previously detailed of the protean aspects and primary or predominant clinical localization

of Hodgkin's disease in practically every organ or tissue in the body, is still ignored in our textbooks and systems of medicine. It was, therefore, the absence of the stereotyped clinical picture of demonstrable primary enlargement of the lymph nodes which warded off the suggestion of Hodgkin's disease in this case, even though the enlargement of the liver and spleen, the secondary anemia, fatigability and dyspnea on exertion and the pruritus pointed to Hodgkin's disease as a possible cause of the paraplegia.

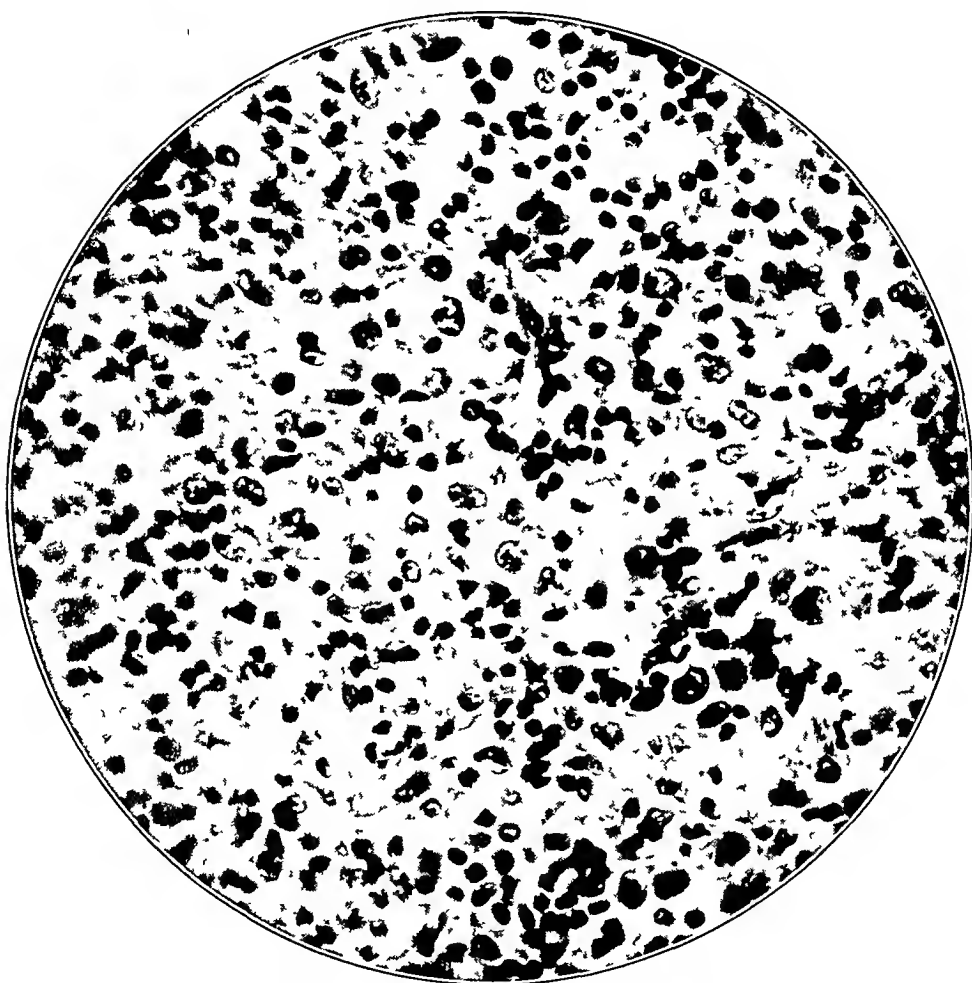


Fig 2 (case 1) —Inguinal lymph node showing hyperplastic cellular stage of Hodgkin's disease

The general problem is one of the most important and fundamental in clinical and institutional medicine, namely, the proper taking of the clinical history by the intern staff of hospitals and medical clinics. In medical institutions, public as well as private, the taking of the clinical history is most frequently if not invariably relegated to the care of the junior or senior intern, whose clinical experience is still immature and incomplete, and whose familiarity with the rarer types of disease

is, to say the least, extremely limited. Furthermore, in the rush of the routine work and the manifold duties devolving on the intern, the patient is not always allowed sufficient time to give a full and detailed account of his symptoms, nor is the intern sufficiently equipped to make a complete investigation of the minor symptoms, which are usually slighted, but which may sometimes be the important ones to give the clue to the diagnosis in a difficult case.

In the case under discussion the initial history obtained by the intern was that of an acute condition with rapidly developing paraplegia. The pruritus of two years' duration and the progressive asthenia, fatigability and dyspnea on exertion antedating the paraplegia did not appear in the early records of the history of the case. Only when the biopsy suggested the pathology of Hodgkin's disease did careful questioning elicit spontaneously the highly suggestive diagnostic symptoms of Hodgkin's disease as detailed in the later published records. The important lesson derived from the study of this case is the need for thorough clinical historical investigation by the experienced members of the visiting and consulting staff of hospitals and clinics. A physical objective examination alone is not always sufficient to establish a correct diagnosis in a difficult case. Certain symptoms registered in the patient's consciousness may be as highly diagnostic or even more so than many objective signs demonstrable to our unaided or even to our aided senses by all the modern laboratory methods of diagnostic precision.

**CASE 2—History**—M. S., a woman, aged 32, was admitted to Montefiore Hospital on April 16, 1925. Three years before admission she began to suffer from migrating pruritus in various regions of her body. The pruritus was intense and marked at night, interfering with sleep. A visible eruption was not present except when it was induced by vigorous scratching. A month or two after onset, she commenced to make the rounds of private physicians and various well known dermatologic clinics. A local skin condition was diagnosed and medication prescribed accordingly. When the remedies failed to relieve, "nervousness" was blamed for the persistency of the pruriginous condition in the absence of any visibly demonstrable skin lesions.

After two years of persistent pruritus, other symptoms began to appear. In April, 1924, she noted slight and painless enlargement of her right cervical lymph nodes. Gradually, she began to develop asthenia and anorexia. In September, 1924, she was suddenly seized with severe pain in her lower cervical and upper dorsal spine, radiating girdle-like peripherally. For three days the pain was acute and recurring, it then lessened gradually. With subsidence of the pain, progressive weakness of both lower extremities developed. At first the right limb felt heavy and weak and later the left. She commenced to stumble, and her gait became dragging. Toward the middle of December, definite paraplegia set in with sphincteric involvement—incontinence of urine and obstinate constipation.

On Dec. 18, 1924, she was admitted to a well known New York institution where physical examination revealed spastic paraplegia with a sensory level at the fourth dorsal segment to touch, pain and temperature. Vibration was lost to the costal border. Position sense was retained even in the toes. There was definite tenderness of the spine in the fourth to the sixth dorsal segment.

Examination of the spinal fluid was negative except for a 3+ globulin reaction. A blood count showed a slight secondary anemia. Roentgen-ray examination of the chest revealed the right diaphragm considerably higher than the left and the superior and posterior mediastinum filled with a large massive shadow probably caused by a new growth which had pressed the heart downward and to the left.

A diagnosis of extradural spinal cord tumor was made, and surgical intervention was decided on. At operation an extensive extradural tumor was found. It reached from the second thoracic laminae to below the fifth. The lower limit was not determined. The gross appearance of the tumor was that of sarcoma. Removal was not attempted.

Following the operation, the patient received several roentgen-ray treatments over the spine without any resulting improvement. On April 16, 1925, she was transferred to Montefiore Hospital.

*Physical Examination*—On admission, examination revealed a well nourished, slightly pale, young woman. Her skin was darkly pigmented but did not present any eruption. There was an enlarged lymph node, the size of a lima bean, in the right cervical region.

The chest showed dilatation of veins in the infraclavicular regions, in the right side more than in the left side. There was marked upper retromanubrial dulness, caused by a large mass in the upper mediastinum demonstrated by roentgen-ray examination. The heart did not present anything abnormal. Her pulses were equal, the blood pressure was, systolic, 110, diastolic, 70.

The abdomen was tense and rigid. The liver and spleen, on percussion, were apparently enlarged. Both lower extremities were spastic, flexed and held in abduction. Both large toes were held in extension, and on touch both extremities began to go into clonic tremor.

On April 27, 1925, cervical lymph nodes were removed for pathologic examination (fig 3). Dr Seecof's report was "Lymph nodes show striking diffuse fibrosis with areas of hyaline scarring. Complete loss of architecture. No germinal follicles. There are foci in which there are densely packed lymphocytes, numerous endothelial cells and an occasional endothelial giant cell. No eosinophils. Diagnosis, Hodgkin's disease, or lymphosarcomatosis." The slide was submitted to Dr James Ewing, whose diagnosis was Hodgkin's disease.

On May 9, 1925, the patient was examined by Dr Abrahamson, who reported "The signs point to a high dorsal transverse myelitis which, in view of the history, is most likely due to Hodgkin's disease."

*Treatment and Course*—The same day high voltage roentgen-ray treatment of the spine and mediastinum was started and repeated until March 10, 1925, three erythema doses were given over each area. The result was slow, moderate recession of paraplegia symptoms toward the end of 1925. The patient had regained control of urination. She could flex and extend her knees and could help herself out of bed on an invalid's chair, but she still showed considerable spasticity of her lower extremities. She was unable to stand up or sit up in bed without supporting herself with her hands. Her rectal sphincteric control had not been regained. The mediastinal mass had receded but slightly.

At present the patient is in excellent physical condition, but mentally she is miserable because of her incontinence, and because she has to remain in bed or be wheeled in a chair.

*Comment*—The chief points of interest in this case are both diagnostic and therapeutic. As in case 1, an imperfect history of an acutely developing neurologic condition led to a diagnosis of a primary spinal cord neoplasm. At operation the tumor was found to be irremovable. Roentgen-ray therapy thoroughly carried out resulted in only

slight relief of the paraplegia. This emphasizes the great importance of early diagnosis and early radiotherapy in Hodgkin's disease, especially when the nervous system is involved. Notwithstanding the fact that the lesions in Hodgkin's disease are among the most sensitive and responsive to radiotherapy, this is true only in the stage of hyperplasia and abundant cellularity. In the late stages of Hodgkin's disease when marked fibrotic changes are present little if any effect can be expected.

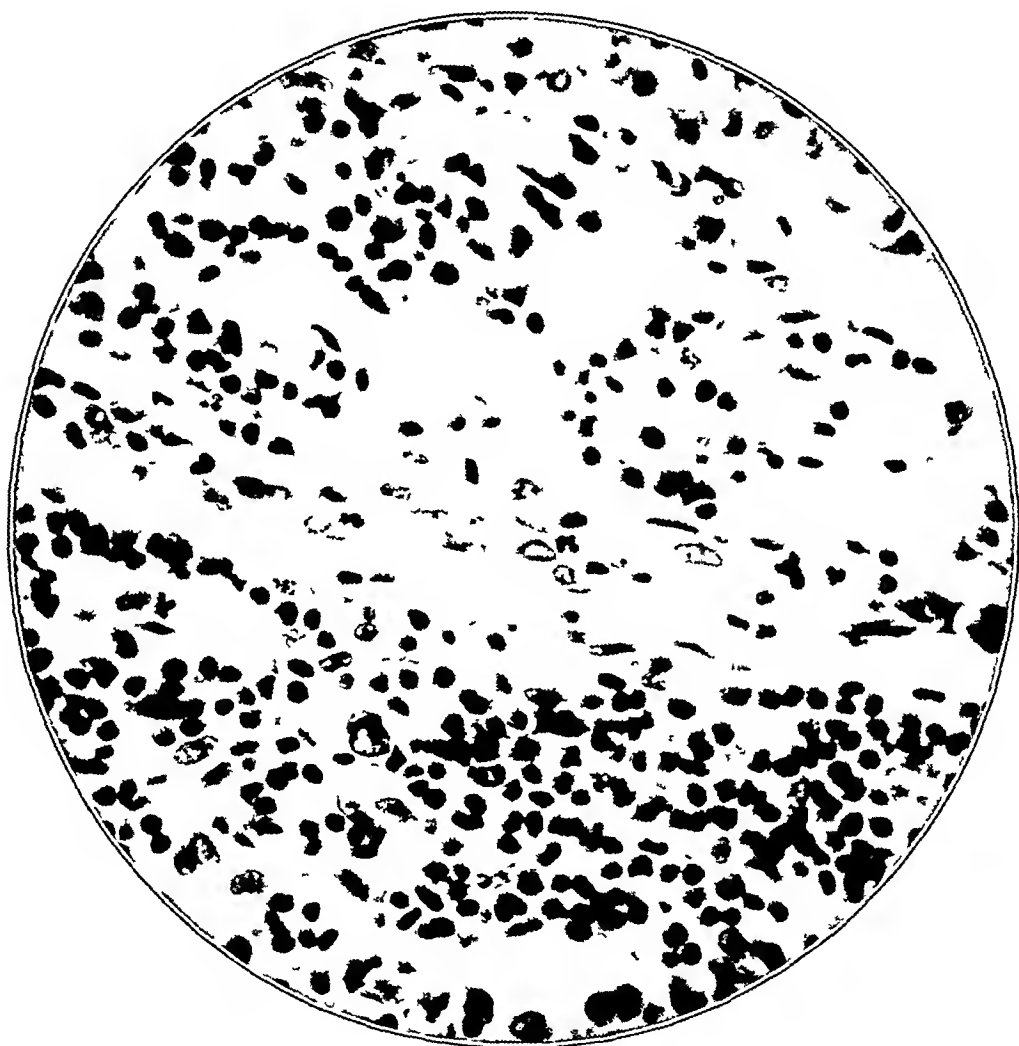


Fig. 3 (case 2)—Cervical lymph node showing commencing hyalinization in Hodgkin's disease

from either radium or roentgen-ray treatments. This is true especially in lesions of the nervous system in which invasion or compression of the nervous elements for any length of time leads to irremediable degenerative changes which may persist even after the original damaging cause is removed.

CASE 3—*History*—A man, aged 29, a patrolman was admitted to Montefiore Hospital, April 13 1922, with a diagnosis of tuberculosis pleurisy with effusion and possibly Pott's disease of the spine. In February 1921 while on night duty

during a heavy snow storm, the patient slipped and fell, striking the lower part of his spine. He was dazed but not unconscious. He lay for a few minutes with his left heel pinned under his spine, unable to rise until he was assisted by pedestrians. He continued on duty during the rest of that night and did not experience any difficulty in walking. The next day the calf of his left leg became swollen and painful. Although he was able to walk, the pain in his leg was considerable, and he stayed away from duty for the next three weeks. He then felt apparently well for several weeks until April, when he was suddenly awakened one night by severe sharp pain in the lower spine radiating laterally to both sides. The pain was most severe over the site of the former injury. For one month it kept recurring, worse at night, interfering with sleep. Toward the end of May, the pain disappeared completely. He felt perfectly well for the next three months until August, 1921, when the pain recurred in a most aggravated form. It was severe and constant day and night. Several physicians were consulted, but the diagnosis was doubtful, and the various remedies failed to relieve. Accordingly, he was admitted to a general hospital in New York City, where he remained under observation for six weeks. A complete study failed to furnish any clue to the underlying cause of his symptoms. Gradually the pain grew agonizing and began to radiate down both lower extremities. Repeated hypodermic injections of morphine had to be resorted to, with but temporary relief.

Discouraged because of the lack of improvement, the patient left the institution to return home. There his symptoms grew progressively worse. In October, 1921, he began to develop signs of spastic paraplegia with sphincteric involvement. In November, he was admitted to one of the largest hospitals in New York City where, after an exhaustive study, a definite diagnosis was not made. The consulting neurologist favored a diagnosis of Pott's disease of the spine, while the consulting orthopedist inclined to a neurologic diagnosis—probably spinal cord neoplasm.

Toward the end of December, 1921, there was a gradual spontaneous return of sensation in the thighs and partial regain of bladder control. In the early part of 1922, there was also partial return of power in both lower extremities.

In March, 1922, when he had recovered almost completely from his spastic paraplegia, he suddenly developed pain in the right side of his chest, accompanied by cough, fever and dyspnea. With the onset of his respiratory symptoms the long delayed diagnosis was finally pronounced as pulmonary tuberculosis with pleuritic effusion and Pott's disease of the spine, and he was transferred to the tuberculosis division of Montefiore Hospital, in the service of Dr. Maurice Fishberg.

*Examination*—On admission, April 13, 1922, the patient was found well nourished and did not appear acutely ill. There was a pleural effusion filling one half of the right side of the chest. The heart was displaced to the left.

Neurologic examination by Dr. Abrahamson revealed a belt of hyperesthesia from the eighth to the twelfth dorsal segment on both sides, most marked from the eighth to the tenth. Below this hyperesthesia there was an area of normal sensation except in the fifth lumbar. The perianal area was normal. Cremaster reflexes were present, which were greater on the left side than on the right. There was constant extensor position of the left big toe. Points of exquisite tenderness to deep pressure and to percussion were present corresponding to the ninth dorsal spine and fourth lumbar. Edema was not present, no gibbus. Vibratory sense was diminished from the knees down on both sides and was lost in the perianal area. There was general motor weakness in the iliopsoas group and flexors of the thighs. There was a slight tendency to foot drop on the right side. There was an overflow incontinence of urine.

*Tentative Conclusion*—This was a lesion of the bone or periosteum at the level of the eighth or ninth dorsal segment with a possibility of a secondary level at the fourth lumbar segment. Whether the lesion was tuberculous, as pleurisy

with effusion might indicate, or sarcomatous, could not be decided definitely without roentgen-ray examination

The next day, April 18, roentgen-ray examination of the spine was negative for bone disease. The chest showed a dense homogeneous shadow occupying the entire right pulmonary field. The middle third of the shadow was slightly denser than the rest. The heart and mediastinal contents were displaced to the left.

On April 26, 1922, Dr. Maurice Fishberg expressed the opinion that, "The roentgen-ray observations are highly suggestive of a mediastinal tumor, the nature and origin of which are undetermined." The same day, for the first time in his life, the patient developed a severe epileptiform convulsion with marked frothing at the mouth and biting of his tongue. During the next few weeks he suffered from dull, frontal headaches radiating to the vertex.

For the first time enlargement of the right supraclavicular and of the left axillary lymph nodes was noted. A biopsy of one of these nodes resulted in a diagnosis of Hodgkin's disease.

*Course of Illness*—The further course of this case, with the exception of one more spontaneous remission of a few months' duration was characterized by symptoms of generalization, marked mediastinal and pulmonary involvement, recurring severe pain in the spine and occasional severe epileptiform convulsions. Three days before his death, the patient developed a low muttering delirium, in which he died.

*Comment*—The remarkable features of clinical interest in this case were (1) the mode of onset with severe pain suggesting at first a traumatic spondylitis and later a transverse myelitis, (2) the repeated spontaneous remissions, (3) the development of mediastinal and pleuro-pulmonary involvement while the spastic paraplegia was apparently clearing up spontaneously, and (4) the repeated attacks of epileptiform convulsions which suggest invasion of the brain.

Until recently all the cases of Hodgkin's disease with epileptiform convulsions failed to show the specific pathologic process in the brain. Within the past few years, Hecker and Fischer,<sup>41</sup> Askanazy,<sup>38</sup> Saalfeld<sup>45</sup> and Holmes<sup>43</sup> reported the definite pathology of Hodgkin's disease in the brain and meninges.

*CASE 4—History*—Y. T., a woman, aged 40, was admitted to Montefiore Hospital on Aug. 14, 1920, and died Jan. 5, 1922.

In March, 1917, she experienced severe pain over the right shoulder. Two or three months later similar severe pain developed in the left thigh. Associated with the pain in the thighs were severe itching and asthenia. Anorexia and loss of weight followed gradually and became progressive.

Two and a half years after the onset of the pain in the right shoulder, evidence of mediastinal involvement and enlargement of the cervical lymph nodes was noted. In December, 1919, the patient was admitted to Mount Sinai Hospital, New York, where a biopsy of a lymph node showed Hodgkin's disease, and roentgen-ray examination revealed involvement of the spine and pelvic bones.

She died with symptoms of generalization on Jan. 5, 1922.

*Autopsy*—This revealed numerous scratch marks on the skin and a large bulging mass on the anterior surface of the vertebral column in the region of the third, fourth and fifth thoracic vertebrae. On section it was found to consist of yellowish, granular, necrotic tissue replacing about one half of the anterior portion of the vertebrae. A large bulging mass present over the right iliac

bone consisted of similar necrotic tissue which almost completely replaced the posterior upper portion of the ilium. On the left, almost the entire ilium, including the acetabulum and a portion of the ischium, was destroyed and replaced by similar yellowish necrotic tissue. The cartilage of the head of the femur was not involved, although flowing freely in a brownish fluid pus. The anatomic neck, however, was eroded.

During removal of the brain, a large bulging mass was found anteriorly and to the left of the cerebellum. On section, yellowish necrotic material was found to replace almost the entire body of the occipital bone and the body of

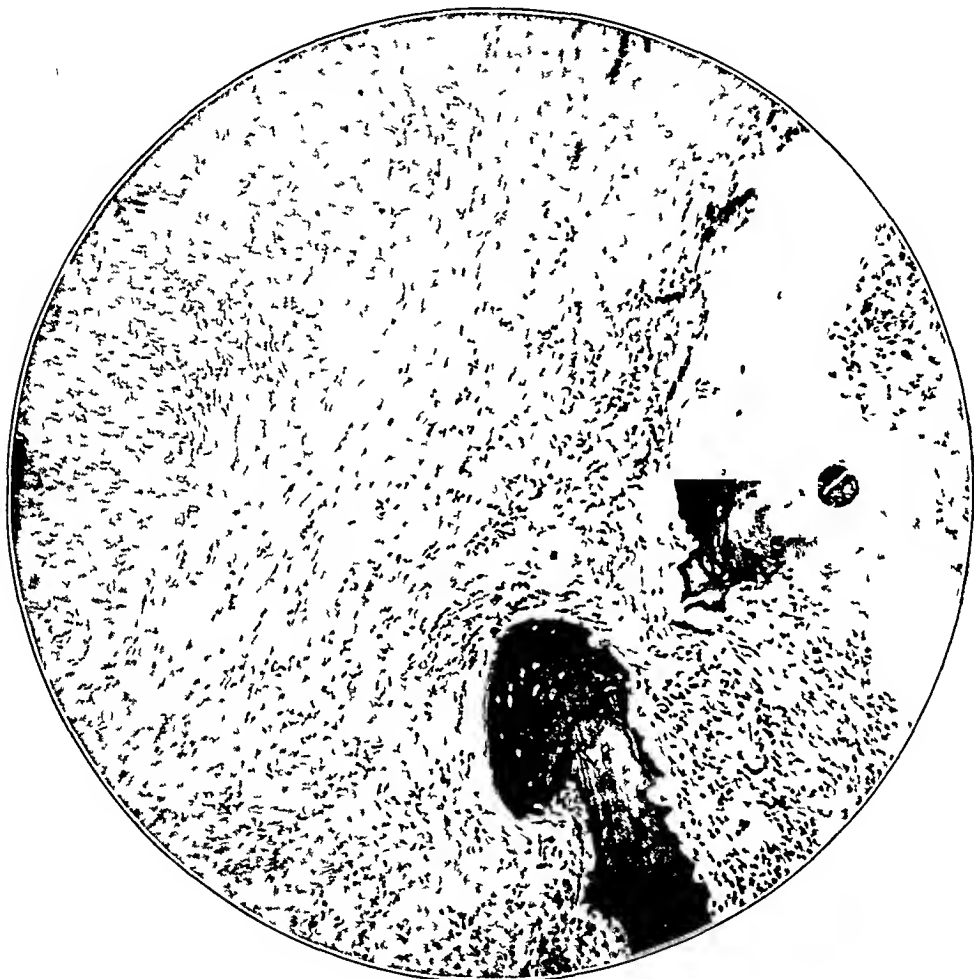


Fig 4 (case 4) —Hodgkin's tumor mass in iliac bone showing necrosis and fibrosis

the sphenoid. The right mastoid was filled with a greenish, purulent material. The brain, on section, did not show any abnormalities.

In addition, lesions were found in the bone marrow, pharynx, muscles, pancreas, lungs, spleen and lymph nodes.

*Microscopic Examination*—Many sections of lymph nodes showed combined lesions of Hodgkin's disease and lymphosarcoma. In some there was marked fibrous proliferation and endothelial cells of the Dorothy Reed type and a few eosinophils, in others, the normal architecture of the gland was destroyed, the lymphocytes closely packed, with little or no fibrosis. In all sections there were large areas of necrosis.

*Comment*—The chief point of clinical interest in this case was the extensive lesions in the osseous system which were probably the first to give rise to the neurologic symptoms of pain in the shoulder and in the thigh two and one-half years before the superficial cervical lymph nodes became enlarged

CASE 5—A man aged 33, was admitted to Montefiore Hospital on April 3, 1918, and died on July 21, 1918

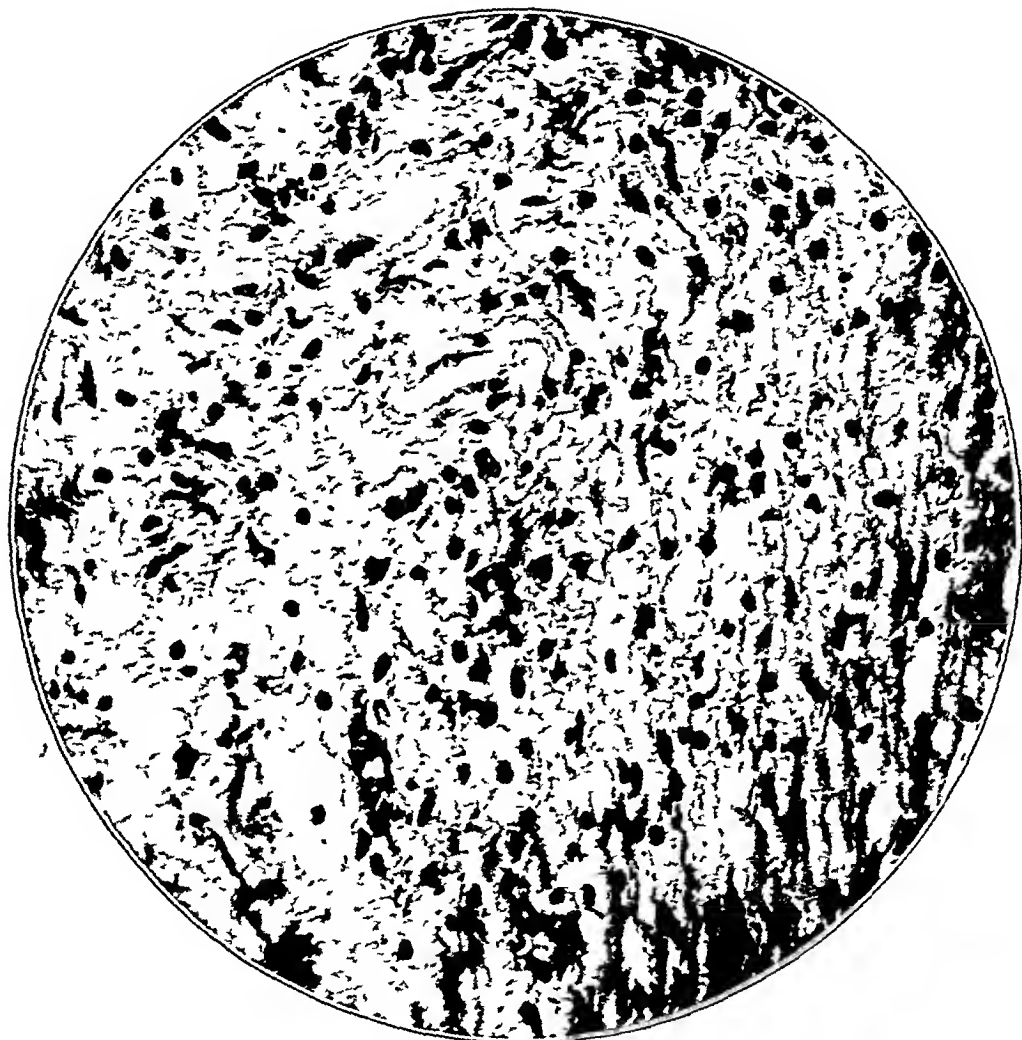


Fig 5 (case 4)—Detail showing high magnification of fibrotic area in Hodgkin's disease of iliac bone

The onset of the present illness was during the early part of 1915 with symptoms of grip followed in a few weeks by excruciating pain in the lumbar region, radiating anteriorly to the abdominal wall. The pain was intermittent and was worse at night. For a period of two years, he made the rounds of private physicians and well known hospitals. The diagnosis was doubtful and the patient failed to obtain relief. In 1917, he was admitted to a large general hospital where a diagnosis of focal infection was made, his tonsils were removed and a few teeth were extracted. When improvement was not noted at the end of a few months, he was sent to Mount Clemens to be treated for supposed chronic rheumatism. There his general health improved and he

gained some weight, but his cervical lymph nodes began to enlarge. This was soon followed by a similar enlargement of his inguinal lymph nodes, accompanied by marked pruritus. He commenced to decline rapidly with signs of generalization of the condition in the chest, abdomen and possibly in the brain. A biopsy of one of the nodes showed "classical Hodgkin's disease."

*Comment*—This case illustrates strikingly how Hodgkin's disease may remain clinically "localized" in an osseous region and give rise to the one neurologic symptom—pain—for more than two years before

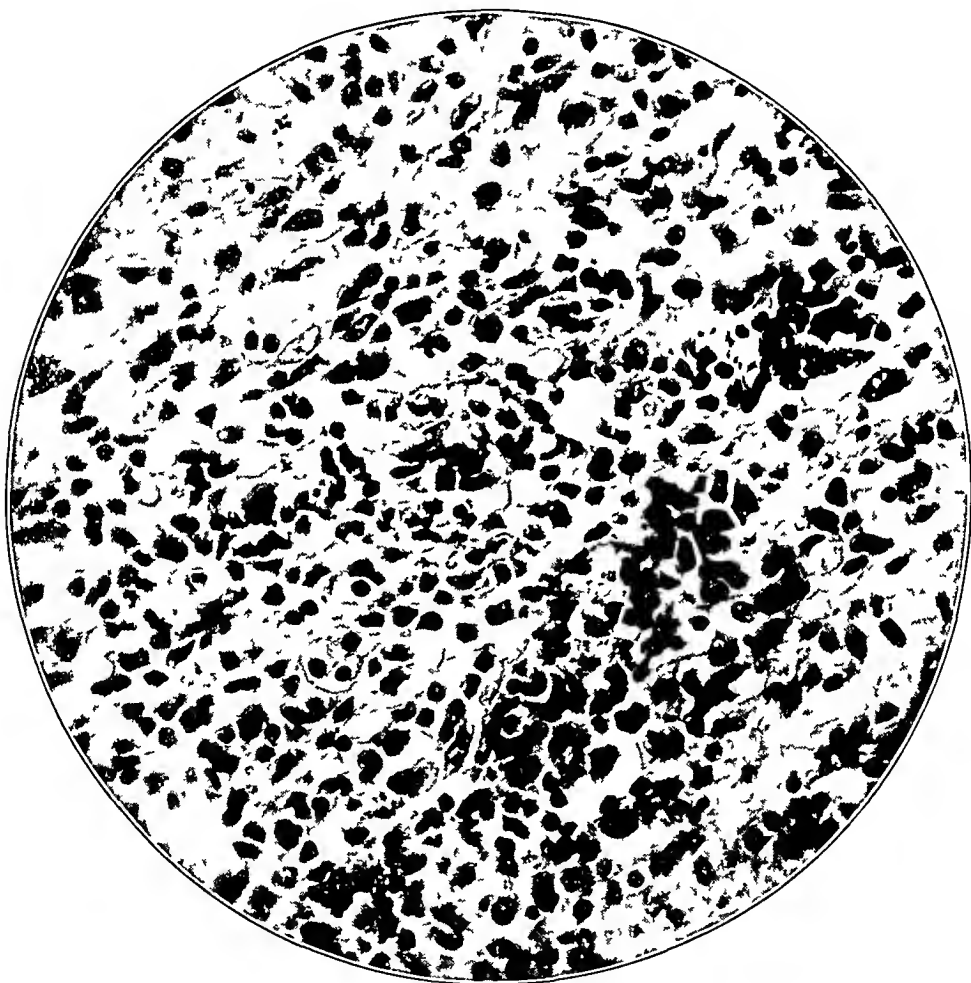


FIG 6 (case 4)—Hyperplastic cellular stage of lymph node in Hodgkin's disease with commencing fibrosis

the appearance of an enlargement of the lymph node and may so strongly simulate a mere local neuritis or arthritis that it may baffle detection even in an institution in which all the modern aids to diagnosis are used

CASE 6—A woman, aged 24, referred in consultation by Dr D Lutinger of New York, was seen for the first time on March 22, 1924. This patient was in perfect health until January, 1923, when her friends noticed that she was los-

ing weight For the next eight months the only other symptom present was a slowly progressive and unaccountable asthenia In August of the same year she suddenly developed simultaneous itching of the soles of both feet In one week this extended upward and involved symmetrically both legs to the knees The pruritus was most intense, especially at night This continued unabated for one month, when she was seized with violent lancinating pain commencing in the left shoulder and radiating down to the finger tips Simultaneously with the onset of the neuralgia she felt the presence of two small lumps in the left axilla In October, she developed severe recurring pain in the epigastrium In November, she became jaundiced A biopsy of one of the nodes showed Hodgkin's disease She ran a progressive downward course, little influenced by radiotherapy Toward the end of her life she, developed herpes zoster and right facial paralysis Autopsy was not performed

*Comment*—The most interesting feature neurologically was the appearance of simultaneous itching in both feet extending to both knees This demonstrates how in some cases pruritus may be caused not by a local skin lesion, but by invasion or compression of sensory nerves at a distance from the site of irritation

CASE 7—A woman, aged 34, was admitted to the hospital on June 11, 1923, and died on April 30, 1924 In the early part of 1917, she commenced to have a dragging pain in the left upper quadrant of her abdomen Several months later, she consulted a physician who found her spleen enlarged The pain persisted for four years until the spring of 1921 At this time, following an acute sore throat, she developed swelling of the cervical lymph nodes followed in quick succession by similar enlargement of the axillary, epitrochlear and inguinal nodes

In July, 1921, she was admitted to Bellevue Hospital, where a biopsy of one of the nodes showed Hodgkin's disease From there she was referred to the Memorial Hospital, where she received radium and roentgen-ray treatments She improved for a while until January, 1922, when she began to develop symptoms of spinal irritation This kept growing slowly but progressively worse for the next sixteen months In April, 1923, a complete spastic paraplegia with sphincteric involvement was definitely established

In June, 1923, she was admitted to Montefiore Hospital There she ran recurring attacks of remittent fever and never recovered from her spastic paraplegia

In July, 1923, she developed a profuse herpetic eruption, at first over the chest region on the upper right side, in the distribution of the level of the third to the fifth dorsal segment, which later spread over the entire body, giving the appearance of typical chickenpox

Consultation with the members of the neurologic and dermatologic staff resulted in a diagnosis of Hodgkin's disease invading the posterior root ganglions, with herpes as a secondary condition

She died with symptoms of profound asthenia on April 30, 1924

Autopsy revealed extensive tuberculosis and retroperitoneal Hodgkin's or lymphocarcinomatosis

*Comment*—Of the many features of clinical interest, I shall emphasize only the apparent primary clinical localization in the spleen four years before the appearance of superficial lymph node involvement, and the importance of treating the spine and retroperitoneum early in the development of paraplegic symptoms

## DIAGNOSTIC CONSIDERATION

A review of the literature and an analysis of thirty-six cases observed at Montefiore Hospital during the years from 1914 to 1925 provide proof of the systemic dissemination and protean manifestations of Hodgkin's disease. These studies, furthermore, furnish incontestable evidence that although in a large percentage of cases the first visible lesions occur in the superficial lymph nodes and spleen, this does not prove the primary localization in the lymph nodes, nor does primary lymph node invasion occur as frequently as is generally believed among physicians. In a considerable proportion of cases, the predominant lesions in Hodgkin's disease, as previously pointed out, apparently may occur primarily and predominantly in any tissue or organ and not only in the glands. Hence Hodgkin's disease may at times simulate a variety of local or systemic disorders and may present great diagnostic difficulties. To arrive at an early tentative diagnosis of Hodgkin's disease in the absence of any enlarged lymph nodes, a knowledge of the protean manifestations of this malignant malady is absolutely essential. In the absence of any specific diagnostic tests for Hodgkin's disease, with the single exception of the characteristic microscopic changes in the microscopic slide, which is not always obtainable, a probable clinical diagnosis can be made only on the basis of a thorough clinical history and a most complete physical examination supplemented by laboratory aids. In a differential diagnosis of Hodgkin's disease of the body cavities or the internal viscera, many diseases will have to be excluded before a probable diagnosis can be made. As the object of the present study was primarily to emphasize the protean nature and the frequency and clinical manifestations of Hodgkin's disease in the nervous system, an attempt will not be made here to enter into a discussion of the various differential diagnostic and clinical criteria of this disease. This has received extensive consideration in the publications previously mentioned, and the reader is referred to them for such information. There is one diagnostic test, however, which is considered exceedingly important to emphasize, namely, the radiotherapeutic diagnostic test. Since the appearance of the original articles of Pusey<sup>48</sup> and Heineke,<sup>49</sup> the exceeding radiosensitiveness of both pathologic and normal lymphoid tissues to radium and roentgen rays has become well known to all students of radiotherapy. The knowledge of this fact has at times been utilized by radiologists to determine whether a given tumor by its ready response to a given dose of radiation is of lymphatic constitution or

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48 Pusey, William Allen. Cases of Sarcoma and Hodgkin's Disease treated by X-Ray, *J A M A* **38** 166 (July) 1902

49 Heineke, H. Ueber die Einwirkung der Roentgenstrahlen auf Tiere, *Munchen med Wchnschr* **50** 2090, 1903, *ibid* **51** 785, 1904

origin<sup>50</sup> In Hodgkin's disease, before extensive fibrosis has occurred, the radiotherapeutic test can be of great help in causing a rapid and decided disappearance or diminution of the symptoms and objective signs of the disease

A therapeutic test of this character may perhaps be objectionable in superficial enlargements or lesions when a biopsy and a microscopic slide may render a positive diagnosis In dealing with suspected lesions of Hodgkin's disease in the internal organs or body cavities, and especially in those of the central nervous system, the radiotherapeutic test not only may determine the radiosensitiveness of the morbid process and thus give a clue to the diagnosis, but also may prove the efficient early means to prevent a paraplegia or a brain lesion

The following case is an illustration of the efficacy of this therapeutic diagnostic test

CASE 8—A woman, aged 27, referred by Dr J Axelrod of New York, was placed in my care at the Van Cortlandt Hospital on Oct 11, 1923 She had an advanced case of Hodgkin's disease of three and one half years' duration On admission she was markedly emaciated and anemic, with dark pigmentation of her entire body The superficial lymph nodes were moderately enlarged There was mediastinal and pulmonary involvement In the upper part of the abdomen there was a large, hard, tender, immovable mass For months before admission she had been running a remittent fever up to 103 F Her condition was considered too far advanced for radiotherapy unless preceded by blood transfusion

Accordingly, on Oct 16, 1923, she was given 500 cc of blood by the Unger method, and the next day a small dose of roentgen-ray treatment was administered to the inguinal region to test the therapeutic response and reaction to radiation She showed slight improvement until Nov 12, 1923, when brain involvement was evidenced by twitching of the muscles of the mouth and periods of aphasia The next day she had a severe, generalized convulsion preceded by a loud shriek The clonic movements lasted a few minutes and were accompanied by frothing at the mouth and biting of the tongue For two days, the epileptiform convulsions kept recurring in severe form Liberal doses of sedatives were administered, without result

A diagnosis of Hodgkin's disease of the left hemisphere of the brain was made The localization was placed in the left frontal area as suggested by the aphasia and the shriek preceding the epileptiform convulsions In view of the general poor condition of the patient and the advanced state of the disease, it appeared probable that any recurring convulsion might lead to a fatal termination As a last resort it was decided to try high voltage roentgen-ray treatment Knowing the exceeding radiosensitiveness of the early and cellular lesions in Hodgkin's disease and their quick response to the intensive use of radium and roentgen-ray treatments, a full erythema dose of high voltage roentgen rays was administered to the left side of the skull in one sitting

The technic was voltage, 200,000,000, filtration, copper 0.5 mm, aluminum 1 mm, milliamperes, 4, target distance, 50 cm, portal, 15 by 15 cm, time, 80 minutes The reaction was profound Within the next twenty-four hours following the irradiation, there was a drop in temperature to 97 F with a considerable drop in pulse rate During the remaining four weeks of the patient's

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50 Blankenhorn, M A Affections of the Mediastinum, *Nelson's Loose Leaf Medicine* 3 578, 1920 Evans, W A, and Leucutia, T Deep Roentgen Ray Exposure as an Aid in the Differential Diagnosis of Mediastinal Tumors, *J A M A* 85 1215 (Oct) 1925

life, she had convulsions only once, on Dec 1, 1923, during the height of excitement of a blood transfusion

*Comment*—The most outstanding point of clinical and radiotherapeutic interest in this case is the apparent response of the brain invasion to one strong therapeutic dose of the roentgen rays. The importance of high voltage roentgen-ray therapy not only as a therapeutic agent but also as a diagnostic test whenever lymphomatous or lymphosarcomatous lesions in the brain or cord are suspected was thus strikingly brought to light

#### THERAPEUTIC CONSIDERATION

In any discussion of the therapy of Hodgkin's disease the following cardinal facts must be kept clearly in view

*The General Nature of Hodgkin's Disease*—As proved abundantly in the text, Hodgkin's disease is not merely a consideration of the lymphatic glands and spleen, but rather a general disease with local manifestations in different tissues and organs in different persons

*The Toxic Element in Hodgkin's Disease*—The toxic element in this disease cannot be ignored. Specific hyperplasia of the reticulo-endothelial elements with or without lymphoid hyperplasia is only one phase and one stage in the pathology of Hodgkin's disease. There are now on record a great number of cases of this disease which ran an acute febrile course with toxic symptoms and then terminated fatally in from several weeks to several months. In these cases the fatal issue was caused primarily not by a proliferative compressive phenomenon, but by a severe toxemia which presented all the characteristics of an acute infectious disease.<sup>51</sup> Although in the chronic forms, the toxic element does not always appear strikingly in the foreground, its unmistakable presence is clearly evidenced in the frequency of the recurring attacks of pyrexia,<sup>52</sup> the progressive anemia and cachexia and the frequently demonstrable foci of necrosis and amyloidosis in the specific lesions of this disease

*Fibrosis and Compression Phenomena*—Extensive fibrosis of the hyperplastic lesions in the late stages of Hodgkin's disease first noted by Hodgkin himself has since been described frequently in the literature as the hard form of the disease. This extensive fibrosis may exist in

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<sup>51</sup> Heissen, F. Zur Klinik der akuten Lymphogranulomatosis, Klin Wchnschr **2** 1640 (Aug) 1923. Levy E. Ein Fall von akuter Lymphogranulomatose im fruhen Kindesalter, Arch f Kinderh **75** 49 (Sept) 1924. Hendricks, W. W. Acute Hodgkin's Disease Following Herniotomy, Internat Clin **3** 217, 1921. Whillington, T. H. Acute Hodgkin's Disease with Involvement of Internal Glands and Relapsing Fever, Quart J Med **9** 83 (Jan) 1916. Howell, A. Acute Hodgkin's Disease, Practitioner **99** 565 (Dec) 1917.

<sup>52</sup> MacNalty, A. S. Lymphadenoma with Relapsing Pyrexia, Quart J Med **5** 58 (Oct) 1911.

fairly large swellings which may press or contract on important organs or structures and give rise to irremediable or fatal compressive phenomena after the active proliferative process has become totally extinct

*Severe Anemia and Cachexia in the Advanced Stages of Hodgkin's Disease*—The toxic factor may cause a severe anemia early in the course of the disease which may simulate a frank pernicious anemia<sup>53</sup> Usually, however, marked secondary anemia and cachexia indicate prolonged toxemia with severe damage to the entire hemopoietic system This frequently is present simultaneously with extensive areas of necrosis and fibrosis in the formerly cellular and hyperplastic specific lesions

*Etiology in Hodgkin's Disease Unknown*—Nearly a century after Hodgkin's first description of the disease, its etiology still remains obscure, and a specific form of treatment has not been discovered<sup>54</sup>

Chemotherapy and surgical intervention, which have been tried out extensively for a number of decades, have proved disappointing either as curative or palliative measures The most efficient local treatment for Hodgkin's disease universally recognized today is of radium and the roentgen-ray treatment The effect of both of these forms of radiant energy is prompt and efficient in influencing the cellular proliferative manifestations of this disease Even bulky growths and infiltrations have been noted to disappear or regress promptly under radiotherapy, with great symptomatic relief not only of the compressive phenomena but at times also of the accompanying toxemia

Although permanent cure has not been reported, prolongation of life for many months and years has been noted by many observers<sup>55</sup>

53 Halix, O (footnote 34)

54 Lubarsch, O Die Lymphogranulomatose, Aschoff's Path Anat **2** 578, 1923 Kaufmann, E Lymphogranulomatose, Path Anat, Berlin-Leipzig **1** 203, 1922 Ewing Neoplastic Diseases, Philadelphia, W B Saunders Company, 1922 Cunningham, W F The Status of Diphtheroids with Special Reference to Hodgkin's Disease, Am J M Sc **153** 406 (March) 1917 Beifeld, A F Present Status of Hodgkin's Disease, Am J M Sc **155** 409 (March) 1918 Cunningham, W F, and McAlpin, K Experiments with Hodgkin's Disease, An Attempt to Produce it in Anthropoids and Other Monkeys, Arch Int Med **32** 353 (Sept) 1923 Lemon, W S Tuberculosis as an Etiological Factor in Hodgkin's Disease, A Historical Review, Am J M Sc **167** 178 (Feb) 1924 Stewart, M J, and Dobson J F Inoculation and Implantation Experiments in Monkeys with Glands from cases of Hodgkin's Disease, Brit. J Exper Path **5** 65 (April) 1924

55 Simmons, C, and Benet, G A Report on the Cases Observed at the Collis P Huntington Memorial Hospital from April, 1913, to July, 1916, with Special Reference to Treatment with Radium and X-Rays, Boston M & S J. **177** 819 (Dec) 1917 Levin, I Action of Radium and Roentgen Rays on Normal and Diseased Lymphoid Tissue, J A M A **77** 930 (Sept) 1921 Schreiner, B F, and Mattick, W L Radiation Therapy in 46 Cases of Lymphogranuloma (Hodgkin's Disease), Am J Roentgenol **12** 133 (Aug) 1924 Stone, W Treatment of Hodgkin's Disease by X-Ray and Radium Based Upon a Study of 200 Cases, Canad Pract & Rev **59** 109 (March) 1924.

(Footnote continued on following page)

However, to obtain the best results with radium and the roentgen rays, radiotherapy must be properly and efficiently applied in the early soft or cellular stages before toxic degeneration has caused extensive fibrotic changes which have converted the lesions of Hodgkin's disease into dense hyaline masses that are just as resistant to radiation as old scar tissue. In lesions of the nervous system especially, prolonged or severe mechanical compression alone even without an accompanying toxic process may result in destructive irremediable degenerative changes.

A fair demonstration of what radiation therapy may achieve in some cases in which paraplegia is present was recently reported by Weber.<sup>42</sup> A patient with Hodgkin's paraplegia was treated with roentgen rays over the site of the lesion. The paraplegia cleared up completely and did not recur within the next five years.

The following two cases are a further illustration of the possibilities and limitations of radiotherapy in Hodgkin's disease with neurologic symptoms.

**CASE 9—History**—A man, aged 46, was referred to the radium clinic of Montefiore Hospital on Feb 6, 1924, with a diagnosis of Hodgkin's disease proved by biopsy. In the early part of 1921, he commenced to have burning and pressure pain in the epigastrium aggravated by food intake. Gradually he began to feel weak but did not lose any weight until the end of 1923. At this time he developed severe pain in his upper dorsal spine and noted bilateral enlargement of the axillary nodes. He consulted a physician, who detected sugar in his urine. A diagnosis of diabetes was made, and no significance was attached to the enlarged lymph nodes in the axilla. Shortly afterward the cervical and inguinal lymph nodes also began to enlarge. He began to lose weight and strength rapidly, and developed a generalized pruritus.

**Examination**—On physical examination the patient was pale and slightly undernourished. All the external superficial lymph nodes were greatly enlarged and in places matted. The result of examination of the chest, lungs and heart was negative. Abdominal examination revealed enlargement of the liver to about 5 cm below the costal margin. The spleen and kidneys were not palpable.

Blood examination revealed red blood cells, 3,520,000, white blood cells, 4,700, polymorphonuclears, 66 per cent, lymphocytes, 28 per cent, eosinophils, 3 per cent, myelocytes, 3 per cent. The blood Wassermann reaction was negative. The blood sugar content was 96 mg per hundred cubic centimeters, urea, 17.1 mg, uric acid, 3.1 mg. Examination of the urine was negative for glucose and albumin.

**Treatment and Course**—On Feb 11, 1924, high voltage roentgen-ray treatment was started and continued until Dec 29, 1924. Altogether forty-four one-half erythema doses were given, averaging forty minutes a treatment.

In April, 1924, the patient developed pain in the lumbosacral region radiating down both lower extremities to the ankles. His legs felt weak. He walked

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Bowing, H. Value of Radium and X-Ray Therapy in Hodgkin's Disease, *J Radiol* **2** 20 (Dec) 1921. Desjardins, A. Radiation Treatment of Hodgkin's Disease with Particular Reference to Mediastinal Involvement, *J Radiol* **1** 161 (Nov) 1923. Chaoul, H, and Lange, K. Ueber Lymphogranulomatose und ihre Behandlung mit Rontgenstrahlen, *Munchen med Wchnschr* **70** 725 (June) 1923. Klewitz, F, and Lullies, G. Beitrage zur Prognose des malignen Granuloms, *Strahlentherapie* **19** 1058, 1924. Desjardins, A, and Ford, F. A. Hodgkin's Disease and Lymphosarcoma, *J A M A* **81** 925 (Sept) 1923.

with a stiff, shuffling gait suggestive of an osseous lesion of the lower part of his spine. There was some tenderness over the lumbosacral region. Gradually, however, as radiotherapy was persisted in, all the symptoms and signs of the disease retrogressed.

Roentgen-ray treatment was discontinued on Dec 29, 1924. The patient was reexamined on Dec 6, 1925. He felt greatly improved in health and strength. During the past six months, he has worked regularly at his former occupation as a painter and has felt well and strong. There has been no reappearance of the superficial glandular swellings. He does not suffer from respiratory symptoms. He can walk up several flights of stairs without dyspnea. Examination of the urine in July, 1925, failed to show any evidence of glucose, although he had been on a full nonrestricted diet for many months prior to examination.

Physical reexamination revealed moderate pallor but no dyspnea, cyanosis or edema. He could stoop forward and touch his toes without discomfort. The superficial lymph nodes were only slightly enlarged, discrete and hard. The heart showed slight acceleration but no other abnormalities. The lungs and abdomen apparently were normal.

*CASE 10—History*—A man, aged 46, was referred to the radium clinic of Montefiore Hospital on Aug 29, 1923, with a diagnosis of Hodgkin's disease, corroborated by biopsy of a lymph node. In August, 1920, three years before admission, he commenced to have pain in both lower extremities on walking. This became progressively worse in character until May, 1923, when he began to suffer from severe upper abdominal pain, cutting in character, radiating posteriorly to the spine. Simultaneously with the onset of his symptoms, he gradually lost weight and strength and became dyspneic on exertion.

*Examination*—The patient was slightly cachectic and emaciated, moderately pale and cyanotic. All the superficial lymph nodes were greatly enlarged, presenting huge conglomerated masses. The parotid and submaxillary salivary glands shared in the pathologic process. Mediastinal involvement was elicited on physical examination and corroborated by roentgenograms. In the upper part of his abdomen there was a large, hard, immovable, tender mass, showing invasion of the retroperitoneal lymph nodes. The liver extended 4 cm and the spleen 8 cm below the costal margin. The patient walked with a shuffling gait as though he had lost the flexibility of the lower part of the spine.

Blood examination revealed red blood cells, 4,800,000, white blood cells, 10,000, hemoglobin, 50 per cent, polymorphonuclears, 68 per cent, lymphocytes, 28 per cent, eosinophils, 4 per cent. The blood Wassermann test was negative.

Roentgen-ray examination of the spine was negative.

*Treatment and Course*—Immediately after admission, high voltage roentgen-ray treatment was started and carried out systematically over the cervical, axillary, inguinal, mediastinal and abdominal regions and over the entire spine. During a period of sixteen months, until Jan 19, 1925, he received altogether fifty-two treatments, each averaging forty minutes. The result was a gradual retrogression of all the lymph nodes and the liver and splenic enlargement. There was moderate recession of the neurologic symptoms and apparently no further progress of the involvement of the nervous system.

The patient was reexamined on Dec 6, 1925, almost eleven months after the last roentgen-ray treatment. His general condition was fair. He presented no definite enlargement of his lymph nodes. His heart, lungs and abdomen apparently were normal. His liver and spleen were not enlarged. His chief complaints were still neurologic pain and weakness of both lower extremities. In spite of his subjective complaints, he was able to be up and about and could stoop forward and touch his toes without difficulty.

*Comment*—As important as the recognition that efficient radiotherapy in Hodgkin's disease can be carried out only in the cellular

hyperplastic stage of the disease is the knowledge that this malady is protean and general in its manifestations. The successful attack on one hyperplastic proliferative focus means only greater vigilance for the stealthy appearance of other pathologic foci in the same or distant regions, tissues or organs of the body. A patient with Hodgkin's disease should remain constantly under expert medical and radiotherapeutic supervision, and the hyperplastic lesions should be treated in their incipency. Only by such close vigilance can the life of the patient best be prolonged and safeguarded. Any general measure must not be neglected, such as dietetic, hygienic or tonic, which will enable the patient to make a more or less successful fight against this malignant disease.

#### CONCLUSIONS

Hodgkin's disease should no longer be defined as a specific enlargement of the lymph glands and spleen with occasional deposits in other viscera accompanied by a severe secondary anemia. It is a specific malignant general disease with protean manifestations in which any tissue or organ in any region of the body may become clinically, primarily and predominantly affected. Pathologically, Hodgkin's disease is characterized by a specific hyperplasia of the reticulo-endothelial elements wherever the invasion of the morbidic agent or process occurs. Since the reticulo-endothelial system is coextensive with the entire body<sup>56</sup> and is not confined merely to, although predominant in, the lymphohemopoietic system, Hodgkin's disease may arise primarily, pathologically as well as clinically, anywhere in the body tissues. The cellular proliferative stage of Hodgkin's disease is only one phase and one stage of the morbid process. Regressive changes—necrosis and fibrosis—are invariable later stages in the development of the disease. Toxemia and anemia are the usual accompaniments of the disease at any stage, although they are most marked as the disease process advances.

The invasion of the nervous system in Hodgkin's disease is by no means as rare as textbooks would lead one to believe. A review of the literature and my own cases have shown that the nervous system may become clinically, primarily and predominantly affected and give rise to symptoms for months and years before the occurrence of any demonstrable enlargement of the lymph nodes or spleen. In a series of thirty-six patients with Hodgkin's disease observed at Montefiore Hospital during the years 1914 to 1925, ten patients, or 27.7 per cent, showed invasion of the nervous system.

Early diagnosis of Hodgkin's disease of the nervous system can be made only on the basis of a thorough and complete study of all the clinical signs and symptoms present in a given case. A neurologic

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<sup>56</sup> Aschoff, L. *Lectures on Path*, New York, Paul B. Hoeber, 1924, p. 1.

examination alone, supplemented even by various laboratory tests directed exclusively toward the nervous system, may prove insufficient to establish a diagnosis. In doubtful cases, therefore, the radiotherapeutic test may prove an important aid in diagnosis. The lesions in Hodgkin's disease before extensive degenerative changes and fibrosis have set in are exceedingly radiosensitive. A quick subsidence of pressure phenomena not only may give a clue to the diagnosis, but also may relieve the patient of an early paraplegia or a brain lesion.

Early diagnosis in Hodgkin's disease of the nervous system is essential to prevent irremediable degenerative changes in the nervous elements.

Radiotherapy, which is the chief measure in the treatment of this malignant disease, must be used early, for in the late fibrotic stages its efficacy is nil. When used early and effectively, it may relieve a paraplegia which may never recur, and thus spare the patient from a condition of incontinence and bed sores lasting through many months if not years.

# PAIRED AURICULAR EXTRASYSTOLES

## SIMULATING INTERPOLATED EXTRASYSTOLES OF SUPRAVENTRICULAR ORIGIN \*

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An electrocardiogram (fig 1) was recently obtained, which on first examination appeared to contain interpolated extrasystoles of supra-ventricular origin. Since such an occurrence, as far as I am aware, has not been demonstrated and furthermore is theoretically impossible, the tracing has been examined more carefully, and a different interpretation has been made.

In an article on interpolated extrasystoles, Myers and White<sup>1</sup> state:

An interpolated beat is a premature contraction of the ventricles which is not followed by a compensatory pause and does not disturb the dominant rhythm of the heart. It is impossible for auricular beats to be interpolated, because auricular premature beats are bound to disturb the dominant rhythm.

One must take exception to the latter phrase, for occasionally one finds auricular premature beats followed by a full compensatory pause.<sup>2</sup> In these instances the auricular premature beat must be so late, and the point from which it rises so distant from the sino-auricular node that the contraction passing over the auricle from this abnormal (ectopic) impulse center fails to reach the sino-auricular node before the latter has started a contraction wave. The two waves meet somewhere in the auricular tissue and come to an end. Meanwhile the sino-auricular node, which has, as is said, discharged itself, proceeds to build up new impulse material at the rate then obtaining in the heart, and starts the following contraction wave at exactly the time it would have if extrasystole had not occurred. Thus the pause is fully compensatory, and the dominant rhythm of the heart is undisturbed.

I do agree, however, with the assertion<sup>1</sup> that interpolated extrasystoles must be ventricular in origin, and that they do not disturb the dominant rhythm of the heart. In the rare instance of an auricular extrasystole which does not disturb dominant rhythm it does, however, take the place of one of the normal contractions, and the tracing shows

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\* From the Evans Memorial

1 Myers, M M, and White, P D. Interpolated Contractions of the Heart with Especial Reference to Their Effect on the Radial Pulse, *Arch Int Med* **27** 503 (April) 1921.

2 Reid, W D. *The Heart in Modern Practice*, Philadelphia, J B Lippincott Company, 1923, pp 59 and 199. Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat*, New York, Paul B Hoeber, 1920, p 221.

merely a single late occurring auricular premature beat. There is not, therefore, a true extra beat, and so no interpolation.

The electrocardiogram (fig 1) shows in leads one and three single instances of runs of three beats which are sufficiently close together to give the central beat the appearance of being interpolated, but an accurate measurement shows that the space (time) between the first and third beats of the run is greater than the sum of any two normal beats, and it is greater than can be accounted for by the slight prolongation of the P-R interval of the third beat. It is evident, therefore, that the last beat in each of these groups occurs at a slightly later time than it should if extrasystole had not occurred. The dominant rhythm is,

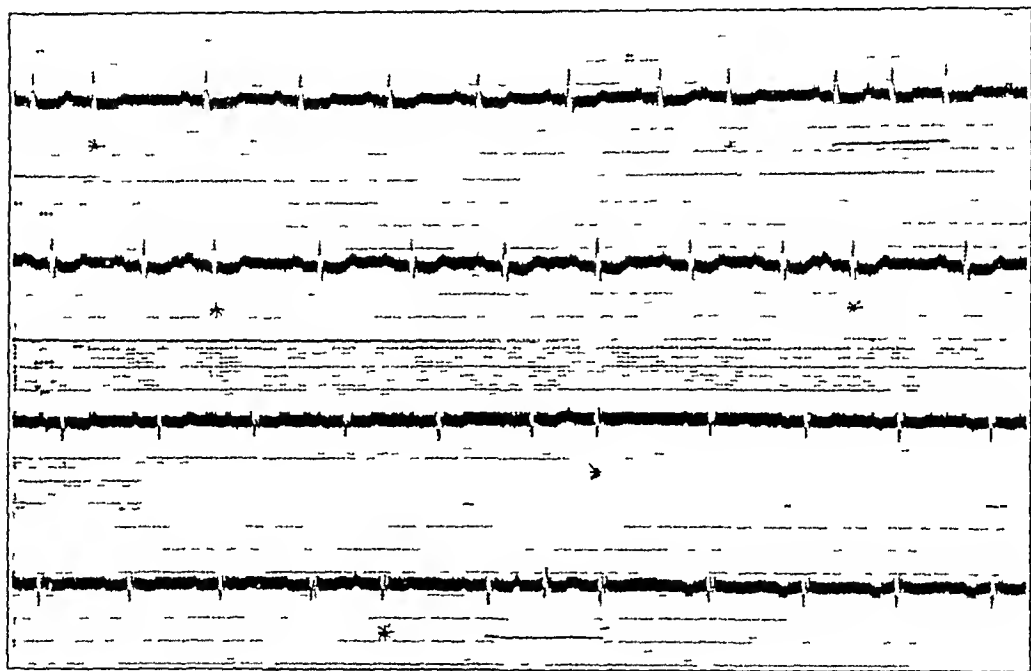


Fig 1—The two runs of three beats, discussed in the text, are indicated by the horizontal line placed below, the single auricular extrasystoles occurring elsewhere in the tracing are marked by an asterisk. The third and fourth strips are from lead 3 and are continuous, the upper being the first half. Coarser abscissas mark off periods of one-fifth second, the finer, of one twenty-fifth second.

therefore, disturbed and, if the criterion that dominant rhythm is not disturbed holds for interpolated extrasystoles, there is, in this electrocardiogram, no true interpolation.

Lead 1 shows two instances of auricular premature beats followed by pauses which are not fully compensatory. Immediately after the pause successive to the second premature beat follows the run of three beats, which makes this lead of interest. The first of the three beats appears to be normal. The second is clearly an auricular premature beat since it is preceded by a P wave that is premature, in fact, it is

superimposed on the T wave of the first member of the group of three beats. The origin of the third beat is less easy to determine. It is introduced by a P wave which is superimposed on the T wave of the preceding heart cycle, and the contour of this P + T wave is such as to prevent a positive decision between the normal and an ectopic point of origin. The P-R interval is lengthened, as is common after interpolated extrasystoles, but this does not favor either point of origin. The beat immediately following this third beat of the run occurs at exactly the normal interval. (This measurement is obtained from the respective P waves since the variation in the P-R intervals disturbs the time of the ventricular complexes.) If this is a premature beat, it is an instance in which the point of origin is so near the sino-auricular node that the latter is discharged practically at once and builds up the material for the succeeding contraction in the usual time.

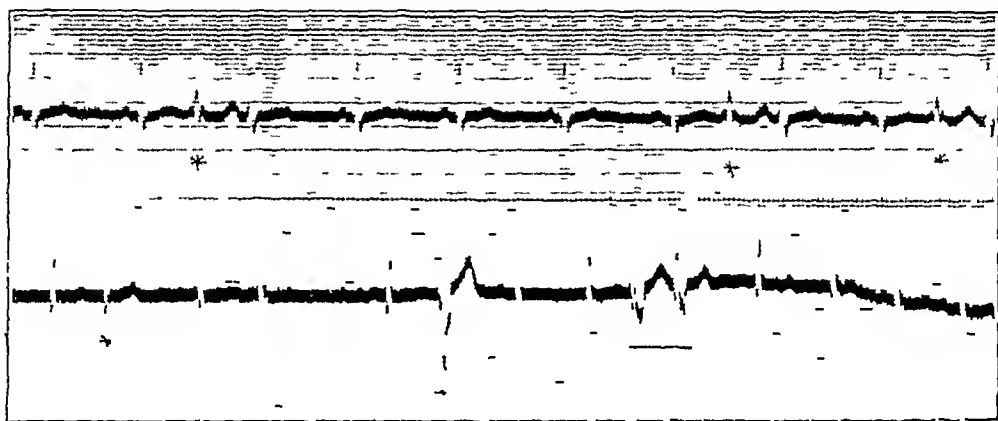


Fig 2—The upper part shows three instances of interpolated extrasystoles, marked by an asterisk. The time marker, it will be noted, was not in operation, but the interpretation of the tracing is not impaired thereby. The lower part shows paired ventricular extrasystoles indicated by a horizontal line placed below, in a tracing of auricular fibrillation. Two single extrasystoles are marked by an asterisk. Time marker as in figure 1.

Lead 3 contains a somewhat similar run of three beats, the interpretation of which is similar to that applying to lead 1, except that the run occurs just at the time of the change from normal to a slower rhythm, probably from the auriculo-ventricular node. Of the three beats of the run I should consider the first one due to the simultaneous contraction of auricular waves starting from the sino-auricular and auriculo-ventricular nodes, respectively. The second appears to be an auricular premature beat and the third is doubtless subject to the same explanation as that given for the third beat in the run noted in lead 1. The slight aberration of the Q R S complexes causes less concern when one notes that similar variations occur elsewhere in lead 3.

The alternative interpretation, namely, that these two runs are really examples of the interpolation of auricular premature beats, may seem more plausible to some readers. It will be found, however, that the third beats were somewhat delayed from their time of expected occurrence when the premature was interpolated. This delay exceeds that explainable on the prolongation of the P-R interval and is rather greater than would appear likely when one adds the factor of sinus arrhythmia, which happens to be present to a slight degree in this electrocardiogram. The interpolation conception forces one to believe that the second wave, the auricular premature, affected the sino-auricular node only in slightly delaying one of its impulses. This seems too difficult to reconcile with

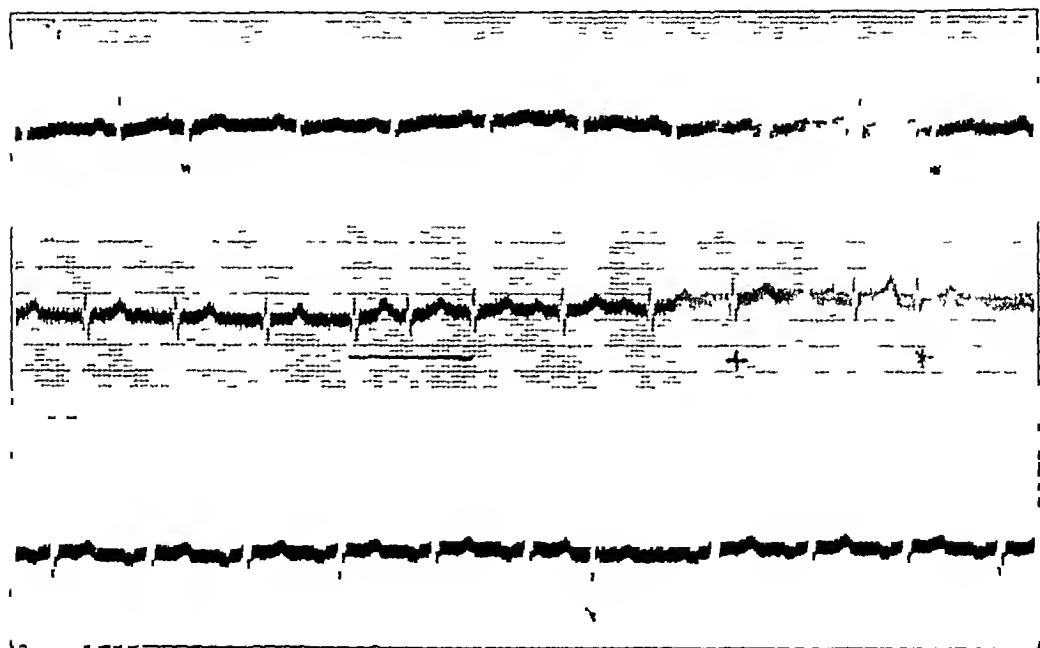


Fig. 3—Tracing obtained two months after that in figure 1. The asterisk and horizontal line are used as in figure 1. Note the run of three beats in lead 2, the disappearance of the depression of the T wave and the return of the P-R interval to normal. Time marker as in figure 1.

cardiac physiology pertaining to premature beats, for it seems accepted that auricular premature beats take the place of one of the beats of the normal rhythm, and the postextrasystolic pause is never less than that following a beat of the normal dominant rhythm. A rare exception to the latter statement occurs in some instances in which the premature beat is near or at the S-A node, and the succeeding heart beat occurs following a diastole slightly less than the normal. It has been suggested<sup>3</sup> that impulse formation has been stimulated so that the S-A node initiates

<sup>3</sup> Lewis, T. Observations upon Disorders of the Heart's Action. *Heart* 3: 279 (June) 1912.

a contraction more rapidly, not so early as happens in the electrocardiogram (fig 1) discussed in this article, however

Figure 2 is introduced to illustrate an instance of true interpolation of a premature beat and to show by contrast how unhesitatingly one may recognize paired extrasystoles if they are of ventricular origin

The history of the patient from whom this electrocardiogram was obtained may be summarized as follows

A woman, aged 64, who was seen in the Outpatient Heart Clinic, had a condition diagnosed tentatively as auricular fibrillation. She was short of breath for about three minutes after ascending one flight of stairs, she walked without untoward symptoms. She said that her health had been satisfactory until recently, and that she did not recall any diseases of etiologic significance regarding involvement of the heart. She had been overweight for years, her present weight was 190 pounds (86.2 Kg), her height was five feet, six inches.

Physical examination showed an obese chest wall, a cardiac impulse just palpable in the fifth interspace at left midclavicular line, no enlargement detected by percussion, no murmurs and marked irregularity in rhythm. The apex rate was 76, wrist 66 and pulse deficit 10. Edema of the legs was not present. The tentative diagnosis was auricular fibrillation.

*Treatment and Course*—Digitalis was prescribed (modified Eggleston method). One week later there was slight nausea, and digitalization appeared complete. The heart showed one and two sound premature beats occurring every four, six, eight or more beats in what appeared to be a regular rhythm. The diagnosis was changed to normal rhythm interrupted by frequent premature beats and digitalis was omitted. An electrocardiogram was taken (fig 1).

Subsequent observation showed the patient to be doing well without digitalis and on a diet rich in vitamins and sufficiently low in calories to induce a gradual reduction in weight.

An electrocardiogram (fig 3) was taken two months later. The disappearance in the depression of the T wave and the shortening of the P-R interval to normal were evidently caused by the absence of digitalis action on the heart. The fact that another run of three beats was disclosed in lead 2 is evidence that this feature is not dependent on digitalis for its presence.

#### SUMMARY

An electrocardiogram is published which at first sight appears to depict interpolated extrasystoles of supraventricular origin.

The interpretation of this tracing is discussed, and the difficulty in differentiating between a true interpolation and pairing of auricular extrasystoles is pointed out.

## Book Reviews

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SCHISTOSOMIASIS VEL BILHARZIASIS By C G KAY SHARP, M D, with a foreword by J B CHRISTOPHERSON, C M G, M D Price, \$2.75 Pp 74 New York William Wood & Company, 1925

Schistosomiasis, the proper title for the condition formerly included under the name bilharziasis, is fortunately rare in North America, but in Asia and Africa it is still a formidable disease. As Dr Christopherson says, it is one of the great endemic diseases of the world, and anything that will emphasize the importance of the parasites and their effects in the minds of the public should aid in the control of the infestation. The work under review admirably answers the needs. Dr Sharp gives a brief but adequate historical account. Bilharz deserves credit for the discovery, and the reason his name is no longer applied to the disease is that some time before Cobbold proposed it, Weiland had named the genus as now recognized by zoologists.

Three disease groups are caused by these trematodes: urinary schistosomiasis, due to *Schistosoma hematobium*, intestinal schistosomiasis due to *S. mansoni*, and schistosomiasis of the Far East, often pulmonary, due to *S. japonica*. Dr Sharp pays special attention to urinary schistosomiasis with which he became familiar in Natal, where many cases occur in natives and Europeans. The intermediate hosts are water snails, and the steps in the discovery of the life cycle are well described by the author.

In the hematuric form, ova are discharged in large numbers in the urine, especially in the morning, and at the end of micturition. As they are 0.16 mm in length and 0.06 mm in breadth, they can be seen with the naked eye. Each ovum already contains the miracidium, and can be quickly hatched in water at 120 F. The miracidium is ciliated, elongated when in motion and tends to become spherical when stationary. They can hatch in the bladder when the urine is diluted, as after taking a glass of beer. Given an opportunity, the miracidia enter the bodies of water snails, become sporocysts, and form daughter cysts in which cercariae develop. The maximum development occurs in the liver of the snail, which may be filled with cercariae. These can be seen wriggling in the sporocysts. They require about six weeks for full development, and when that occurs, they bore their way through the tissues of the snail into the respiratory organs or the intestinal canal and so reach the water. Dr Sharp gives brief but clear descriptions of the pathologic change and morbid anatomy of the various forms of schistosomiasis. Cirrhosis of the liver is one of the most interesting, and the cases seem to give a high percentage of primary carcinoma. Little is known of immunity. The signs and symptoms are fully described. The definite diagnosis depends on the discovery of the ova in the urine. The author uses a concentration method, pouring off the water after successive centrifugalizations. Death is rare, the disease continuing for months with little inconvenience to the patient, it may even last for many years. Septic diseases and malignant changes are not infrequent. Living ova may be expelled during the entire period of infection, having been found by Christopherson as long as twenty-eight years after its beginning.

The author gives a general review of the treatment of schistosomiasis in different parts of the world. Mass treatment by antimony tartrate is a valuable prophylactic, but education to check infection and reinfection and destruction of infected snails should be attempted. Dr Sharp gives selected references to the extensive literature. The book is well printed on good paper. The few illustrations are adequate but the price seems to set a record for seventy-four small octavo pages. This would seem to lessen the circulation of a work that should be in the hands of health officers and practicing physicians over a

large part of the world. It would seem more economical to publish such works in periodicals or reports of institutions.

THE PHYSIOLOGY OF THE CONTINUITY OF LIFE. By NOEL PATON, M.D., B.Sc., LL.D., F.R.S., Regius Professor of Physiology, University of Glasgow. Pp 226, with subject and author index, and 78 illustrations. London: The Macmillan Company, Limited, 1926.

This is a short monograph on the physiology of reproduction and inheritance from the standpoint of a physiologist. The book is based on lectures delivered to the students in physiology in the University of Glasgow during the past five years. The author assumes that the reader has some knowledge of chemistry, zoology and general physiology. He presents and attempts to criticize and analyze theories and facts in the large and important fields of inheritance and reproduction. He says in the preface "In every branch of physiology there is the tendency to give and accept *ex cathedra* teaching, which is soul destroying alike for the teacher and the student. Perhaps in no part of physiology is the tendency to authoritative teaching more seen than in that which concerns reproduction and inheritance. Certain conclusions have been generally accepted as *choses juges*, about which further discussion is deemed unnecessary, but, upon examination, many of them are found to be mere hypothesis. The dictum that life can only arise from life, the so-called mendelian laws of inheritance, the part played by chromatin in inheritance and in the determination of sex and the impossibility of the transmission of acquired characters may be cited as examples."

This quotation gives a clear idea of the author's point of view throughout the monograph. He does not always seem successful, however, in carrying this view into operation, at least the success of the author varies greatly in the different chapters.

The book is divided into nine chapters on life and heredity, reproduction, sex, the determination of sex (two chapters), the relationship of the germ cells to the somal cells, the influence of the gonads on the soma, the influence of the soma on the gonads, sexual life, the nutrition of the zygote before birth (pregnancy), parturition, the nutrition of the infant—suckling and milk secretion. These chapters are of unequal value in completeness of statement and in critical evaluation of the data. For example, the chapter on parturition seems incomplete, both in statement of facts, in description of processes and in analysis of factors involved. The volume nevertheless brings together scattered data in the fields of botany, zoology, physiology and internal medicine in a helpful and lucid presentation. The volume will be of value to physicians and other students of the biologic sciences.

MODERN MEDICINE, ITS THEORY AND PRACTICE, IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS. Edited by SIR WILLIAM OSLER, ed 3 revised. Re-edited by THOMAS McCRAE, assisted by ELMER H. FUNK. Volume 3. Pp 1052 with illustrations. Price, \$9. Philadelphia: Lea & Febiger, 1926.

This volume contains a series of excellent articles thoroughly revised to date on the diseases of metabolism and the digestive system. The chapter on metabolism by Eugene F. Du Bois is of especial value to the practitioner. The scientific data of this broad and still incomplete subject are presented so clearly as to be readily grasped by the average clinician. The chapters on diabetes, diabetes insipidus and gout by Thomas F. Fitch are authoritative and complete. A general discussion by Charles G. Stockton of the physiologic and anatomic factors which enter into an understanding of the diseases of the digestive tract opens the section devoted to gastro-intestinal diseases. The splendid chapter on the diseases of the mouth and salivary glands originally written by David Riesman has been revised by Henry K. Mohler. The chapters

on diseases of the esophagus by Chevalier Jackson and Louis H. Clerf, on functional diseases of the stomach by Julius Friedenwald, on organic diseases of the stomach by Charles F. Martin and Colin Sutherland, on diseases of the intestines by Alfred Stengel and on diseases of the pancreas by Eugene L. Opie are likewise authoritative and complete. The chapter on diseases of the liver, gallbladder, and biliary ducts by the late A. O. J. Kelly, has been revised by B. B. Vincent Lyon. It contains much of interest concerning the function of the liver and gallbladder, a discussion of the various functional tests of the liver, including the van den Bergh test, is included. The discussion of nonsurgical drainage of the biliary tract is of interest, although the diagnostic and therapeutic value of this procedure is questioned by many internists, because of the author's position as the foremost advocate of its use. Only a short paragraph is devoted to cholecystography as developed by Graham, a method which has clarified the diagnosis of gallbladder disease in a remarkable manner, and which is among the foremost achievements of medicine during the past decade. The admirable chapter on sprue by Edward Jenner Wood should be read by all American physicians, since the disease occurs in this country, is little known, and since it is likely to be confused with pernicious anemia. The original chapter on diseases of the peritoneum by Sir Humphrey Rolleston has been revised and remains an excellent portrayal of this subject. The volume, on the whole, maintains the high Oslerian standard set for the complete work and deserves a place in every medical library.

ABHANDLUNGEN AUS DEM GESAMTGEBIET DER MEDIZIN. DER HEUTIGE STAND DER LEHRE VON DEN GESCHWULSTEN. By CARL STERNBERG. Price, 65 cents. Pp. 136, with 21 illustrations. Second edition. Vienna. Julius Springer, 1926.

This second edition of Sternberg's brief manual is one of a number of similar works by members of the faculty of the University of Vienna. A little more than one-half is devoted to the general subject and the remainder to a brief account of separate varieties of tumors.

Both portions are complete, well written and carefully epitomized to handbook proportions. The work is so modern that the recent and somewhat sensational work of Gye has a judicial and judicious review. The work of a few American investigators receives creditable mention. Omissions of any reference to other American work, that by Mallory on dural fibromas, for example, is in thorough accord with the general failure of European writers to consider American research, this neglect, however, is not so marked as in former years. The monograph on melanomas by the English pathologist Dawson is not mentioned.

In the second portion, the care with which undecided matters are dealt is highly satisfactory. As examples, the origin and classification of growths such as the small yellow epithelial tumors of the appendix so opprobriously named "cancroid" and the tumors thought to be primarily from the peritoneum may be cited. Sternberg states definitely that the leukemias, lymphogranulomatosis, chloromas and myelomas are not to be regarded as tumors (blastomas).

The illustrations are carefully selected and are only of gross appearances. The bibliography is a rich mine of "source-material" for a work so abridged. Students who read German will find pleasure in this account of tumors as well as a large amount of authoritative information concisely stated.

COLLECTED PAPERS, HENRY FORD HOSPITAL, DUBLIN, MICH. Price, \$8. New York. Paul B. Hoeber, 1926.

Like any book compiled of collected papers, this volume contains many current articles on more or less unrelated subjects. The main portion of the work is comprised of forty-three articles by members of the staff of the Henry Ford Hospital covering a period of ten years, from 1915 to 1925. With few excep-

tions, notably the articles by McClure on "The History of Transfusion of Blood" and "Permeious Anemia," the contributions are taken from the recent literature. The major portion of the work which is presented in some of the articles was done at institutions other than the Henry Ford Hospital. In nearly all instances, the articles are reprinted from journals of well recognized high standing, so that many of them have been reviewed previously.

The contribution by Davidson on "Tannic Acid in the Treatment of Burns" is worthy of special note. His conclusions are conservative and seem to be well warranted by the theoretical and practical evidence presented. The preliminary report on "Immediate Metabolic Disturbances Following Deep Roentgen-Ray Therapy" by Doub, Bolliger and Hartman, has, in the light of subsequent contributions, been the basis for some new and rather promising developments. The work of Mason and others on tissue extracts and tissue autolysis, and that of Plass and his associates on blood chemistry in the toxemias of pregnancy, form two groups of interesting and helpful papers.

As a whole, it seems that the articles contained in this volume compare favorably with other similar collections.

HISTORY TAKING AND RECORDING. By JAMES A. CORSCADEN. Pp 78. Price, \$1.50. New York: Paul B. Hoeber, 1926.

Any method that may serve as a stimulus to better history taking and recording is of particular interest to those concerned with the teaching of physical diagnosis. Mastery by the student of the technic of history taking is of such great importance that many attempts to clear the way have been made through the medium of handbooks. This text of seventy-eight pages designed for the student includes a discussion of the general principles of case history writing and an extensive list of terms employed, classified according to the regions of the body and the diseases commonly located in those regions. Suggestions as to form and outline should clarify the objective sought in a reliable history, so far as they are stimulating to the student, they will serve a useful purpose. Since, however, a medical history reflects the general medical experience and attainments of a physician, a handbook cannot entirely solve this problem. This little book should be as valuable as any in providing the foundation for a good history.

THE SURFACE EQUILIBRIA OF BIOLOGICAL AND ORGANIC COLLOIDS. By LECOMTE DU NOUY. American Chemical Society Monograph Series. Pp 212. Price, \$4.50. New York: Chem. Catal. Co., 1926.

This monograph by du Nouy with introductions by Alexis Carrel and Robert A. Millikan, concisely presents eleven chapters on surface equilibria as follows: technic, drop of the surface tension of colloidal solutions as a function of time, monomolecular layer of serum constituents, sodium oleate, egg albumin, characteristics of immune serum, influence of colloids on the crystallization of sodium chloride, surface equilibrium of complex colloidal solutions, interfacial tension, colloidal solutions of proteins, serum and plasma, general conclusions. That a monograph has won the approbation of so eminent a physicist and biologist, stamps it as a contribution of first rank. Although all of the applications of this work may not be apparent now, the author in quoting from Claude Bernard, does "open up a new road."

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## WEIGHT AND PHYSICAL MEASUREMENTS AFTER THYROIDECTOMY

RAPID CHANGES IN WEIGHT REFLECTED IN PHYSICAL MEASUREMENTS ON ADULTS AFTER THYROIDECTOMY<sup>1</sup>

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### CONSTANCY OF AN ADULT'S BODY WEIGHT

Body weight during adult life is constant to a noteworthy degree, notwithstanding the fluctuations which occur during physical exercise and the variations in the diet<sup>1</sup>. As yet few people follow the regimen of the person who has been treated for diabetes, who weighs or tries to estimate carefully the portions of food taken, even though the country does show signs of becoming calorie conscious. Man normally eats what he wants, and as much as he wants if he can get it. Nevertheless, it is more than common to hear such expressions as, "I have hardly gained or lost a pound in the last fifteen years," or, what is slightly more an exact self-observation, "I have gained only a little and that very slowly." This fair constancy of the individual is in contrast with the wide variations in weight shown by the different men and women in any large group that may be measured.

### VARIABILITY OF WEIGHT COMPARED WITH OTHER BODY MEASUREMENTS

Of all the gross physical measurements frequently made, that of body weight gives the greatest variability within the group. This is to be expected, as weight is a cubic measure whereas the others are linear or cross-sectional measures. The range found in weight for a thousand men cannot be compared directly with the range found for stature in the same persons. The units are not of the same kind. To secure a

<sup>1</sup> From the Department of Psychology, Stanford University, Calif., and the New England Deaconess Hospital, Boston, Mass.

<sup>1</sup> DuBois, Eugene, F. Basal Metabolism in Health and Disease, Philadelphia, Lea and Febiger, 1924, p. 181.

basis for direct comparison is, however, a simple matter. It is necessary to find only the average variation, or better the standard deviation, for the series of weights and to divide this by the average or mean weight for the group. A similar computation is made for the measurements of weight. Then there are two so-called "coefficients of variation" which are given in terms of percentage and freed from the original units of measurement.

For a better understanding of such comparisons and their importance, we may refer to extensive data published by Davenport and Love.<sup>2</sup> We include in table 1 a simplified revision of a table in which they give a summary of dimensions of approximately 100,000 white troops at demobilization in 1919. In this table it will be found that the extreme coefficients are those for height and weight, 3.9 and 11.7 per cent, respectively. The original table contains data for nine other measurements which we have not included. Height has a coefficient just a trifle smaller than sitting height in their table, and these are definitely lower than any other physical measurements presented, although there are ten other measures of a linear character, i. e., either length or diameter. Weight shows the highest percentage of variability. Circumferences, in general, range about midway between these extremes. It is not necessary to consider each one of these measures separately. The technic of taking them has some bearing on the results. The point that needs to be stressed is that such physical measurements vary from each other in a characteristic manner. As adults, we are most alike in stature and least alike in weight.<sup>3</sup>

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2 Davenport, C. B., and Love, A. G. *Army Anthropology*, Washington, D. C., Gov't Printing Office, 1921, p. 234, table 103.

3 The reader may be inclined to criticize the use of army data in this connection, as height is a qualifying consideration in selecting soldiers. The extreme lower statures do not appear in their normal frequency in the data on army anthropology, but this fact does not destroy the fundamental nature of the comparison stressed in the foregoing. Harris and Benedict (*A Biometric Study of Basal Metabolism in Man*, Carnegie Inst. Wash. Pub. No. 279, Washington, 1919) in table 9, on page 54, cite from various sources a large amount of data on stature for men and women. They give data for seventeen different groups of men—students, convicts, persons of various nationalities and others. The coefficients of variation range from 3.66 to 4.3 per cent and give an average of 3.88 per cent. From the literature they have compiled data on ten groups of women. Here the range of variation is from 3.7 to 4.4, and the average is 4.08 per cent for stature. The number of series of body-weight results available for comparison is decidedly more limited. No doubt can exist, however, that weight is a much more variable character than is stature. No group of weight data that we have been able to find shows a variability as small as 10 per cent; in some groups it is as high as 25 per cent. Our own data on patients with diabetes (Root and Miles, *Physical Measurements of Diabetic Patients*, J. M. Research 2:173, 1922) may be cited in this connection. For seventy-seven men with diabetes the average height was 171 cm., with a variability of 3.5 per cent, average weight, 61.2 Kg., with variability of 15.4 per cent. The fifty-six women with diabetes had an average height of 159 cm., with a variability of 2.9 per cent, the weight was 53.9 Kg., with a variation of 19.7 per cent.

It is the usual practice to measure a person's height as the easiest measurement to make, and on that basis to estimate what he should weigh. For this estimation a "height-weight table" is used which commonly takes into account no other factors than sex and age.<sup>4</sup> It seems to us a curious and an indefensible position to make that one particular linear measure in which we are most alike the basis, often the sole basis, for predicting the normal value for a factor which exhibits the most marked deviation even in an homogenous group of physically fit soldiers.

TABLE 1—"Army Anthropology" Data on 100,000 White Troops Showing the Coefficient of Variation for Different Physical Measurements

Part Measured*	Average Observed Value	Standard Deviation	Coefficient of Variation, per Cent
Body weight (kilograms)	65.6	7.7	11.7†
Height	172.0	6.7	3.9
Sternal notch	141.2	5.0	4.2
Sitting height	90.4	3.5	3.9
Spin	175.6	7.0	4.5
Shoulder width	41.8	2.1	5.8
Pelvic transverse diameter	29.1	2.8	9.7
Depth of chest	21.6	1.0	8.7
Transverse diameter of chest	29.0	2.1	8.3
Girth of chest	88.8	5.1	5.7
Girth of waist	77.9	6.0	7.7
Circumference of thigh	52.7	3.7	7.1

\* All values are given in centimeters except body weight, which is in kilograms.

† As published (table 103, page 234), Davenport and Love give the coefficient of variation for weight as 3.587 per cent. This is a mistake without doubt for no such value is characteristic of weight measurements. Curiously, a similar mistake is made in their table 104 for colored troops. Harris and Benedict, page 58, refer to nine groups of weight data, not their own, and the coefficients range from 10.4 to 25.1 per cent. In their own group of data, their table 2, the coefficients of variations for weight range from 11.2 to 20.3 per cent.

#### CORRELATION OF BODY WEIGHT, HEIGHT AND CHEST CIRCUMFERENCE

If, in conformity with the old myth, man's shape were perfectly spherical, and if all men were equally dense, then the person with the greatest height or width, whichever we choose to call it, would weigh the most. There would be perfect correlation between stature and weight or waist diameter and weight, or circumference and weight, etc. It is, of course, a fact that as correlations go in biologic material, there is a high degree of positive correlation between height and weight, taking man as he is found. In 1899, Pearson pointed out that this correlation for English undergraduate students, expressed in figures, was  $+0.49$ . In the data on army anthropology referred to in the foregoing, it was  $+0.48$ . The many correlations between height and

4 The Life Extension Institute, Inc., New York, publishes (form 521), a table entitled "The Ideal Build" in which they make the statement that "gain in weight with advancing years, beyond age 35, is not physiologic." They recognize three main types of skeletal framework: slender, medium and massive. The latter is allowed from 10 to 15 per cent increase over the values given in their table. The "slender" are allowed a reduction of 10 per cent.

weight that have been made in groups of children or persons well within the growth period are not pertinent to our discussion. There are, however, considerable data on adults that verify this rather high correlation. For example, the data of the Nutrition Laboratory, so carefully treated by Harris and Benedict<sup>5</sup> show the following correlations between height and weight: 136 men,  $+0.57 \pm 0.04$ , 103 women,  $+0.33 \pm 0.06$ . They found, furthermore, that when partial correlations were computed so as to eliminate the influence of age as a factor, the values of these constants were but slightly modified.

The fact that height and weight are positively correlated in a striking degree is, of course, significant, and may not be denied, but the presence of a positive correlation is no warrant in itself for making one factor the sole basis for predicting normalcy in the other. We are not spherical. Other measures than height must be taken into account, especially since we have found that these other linear measures (skeletal widths) vary more from person to person and so necessarily exercise a greater influence in determining what is essentially the cubic contents of the body. The desirability of introducing into the prediction basis for weight some factor in addition to height and age was urged long ago by Bornhardt, the Russian military surgeon. Recently Dreyer,<sup>6</sup> and particularly Gray,<sup>7</sup> have written on this question. Gray has performed important service in regard to the whole problem of weight prediction by his critical reviews of the earlier literature and by comparisons of results secured when predicting weight by different standards. In our article on the physical measurements of patients with diabetes,<sup>8</sup> we emphasized this point but showed that chest circumference recommended by some as the needed factor clearly was not appropriate. The correlation between the circumference of the chest and the weight is much higher than it is for stature and weight. These correlation values for girth of the chest and weight range from about  $+0.65$  to  $+0.95$ . The circumference of the chest is an overall cross-sectional measure. It is a second power measure of that for which body weight is a third power measurement. Accordingly, they will correlate conspicuously, for we are measuring practically the same thing, in one case in centimeters and in the other in kilograms. The plump person having a large cross-sectional area on the basis of the circumference of his chest makes for

5 Harris, J. Arthur, and Benedict, Francis G. *A Biometric Study of Basal Metabolism in Man*, Carnegie Inst., Wash. Pub. No. 279, Washington, 1919, p. 59, table 12.

6 Dreyer, G., and Hanson, G. F. *The Assessment of Physical Fitness*, London 1920, reprinted by Hoeber, New York, 1921.

7 Gray, H., and Mayall, J. F. *Body Weight in Two Hundred and Twenty-Nine Adults. Which Standard is Best?* *Arch. Int. Med.* **26**: 133, 1920; Gray, H., and Root, H. F. *Weight Prediction by the Formulae of Bornhardt, of Von Pirquet, and of Dreyer*, *Boston M. & S. J.* **185**: 28, 1921.

8 Root, H. F., and Miles, W. R. *Physical Measurements of Diabetic Patients*, *J. M. Research* **2**: 173, 1922.

himself an "ample standard, and we "predict as normal" nearly that which we find him to be in weight." Surely this is absurd and dangerous, as it befores the whole question.

What is much needed at present is a clearer understanding of the relationship between the physical measurements that may be practically taken on an adult man or woman, and the marked fluctuations in the body weight of adult persons. What measures, consistently and pronouncedly, reflect gain or loss of weight independent of the factor of growth? What measures show a high degree of stability in the face of such changes in weight in the adult? It seems to us that only on the ground of such information can progress be made. Unfortunately, with all the measuring that has been done on living man, little concerns itself with this question. Before presenting the data which we have collected on a small group of adults with hyperthyroidism in whom rapid weight changes followed operation, certain other related material should be reviewed.

#### CHANGES IN BODY MEASUREMENTS DURING SEVERE UNDERNUTRITION

In 1915, Benedict<sup>10</sup> published his important study of prolonged fasting. This investigation was conducted at the Nutrition Laboratory in Boston from April 10 to May 14 1912. The subject of the thirty-one-day fast was Mr. A. Levanzin of Malta, a man 40 years old. He was close to average weight for his height judged by the Medico-Actuarial Standards of 1918. Dr. H. W. Goodall, the physician who repeatedly made physical examinations of Levanzin during the fast, had this to say as a summary on the patient's physical condition:

"The general appearance of the subject remained good throughout the period of observation. A gradual loss of body tissue was evident, but the changes were not marked from day to day. The most pronounced change was in the abdomen, which became flat as soon as he ceased to take food and was distinctly retracted after the fifth fasting day. This for the most part appeared to be due to the prompt disappearance of gas in the intestines. The actual loss in body tissue appeared to be quite evenly distributed over the body, but was most noticeable in the tissue of the back of the neck, in the sinking in of the supra- and infra-clavicular spaces, and in the prominence of the ribs. The muscles of the extremities, which were moderately firm at the beginning of the fast, appeared to have softened to a slight degree."

An elaborate series of anthropometric measurements was made on Levanzin under the direction of Dr. W. L. Anderson of Yale. This series included mostly measurements of girth. Such measurements of breadth as were used were not started until the twelfth day of the fast.

9 Gray and his collaborators, Mavall and Root, found that the Bornhardt and the Dreyer Methods, which advocate the use of chest circumference, give prediction results closer to actually observed weights than do other methods.

10 Benedict, Francis G. *A Study of Prolonged Fasting*, Carnegie Inst. Wash. Pub. No. 203, Washington, 1915.

Table 2 is compiled from data given by Benedict (see his page 68) and our own computations of these data. Values are given for various physical measurements taken on Levanzin just prior to the fast and again on the thirty-first day of the fast<sup>11</sup>. The percentage of loss is computed on the basis of the preliminary value in each case. He lost 21.8 per cent of his original weight, but there was no change in height. The depth of the abdomen decreased 19.1 per cent (see Goodall's statement), but there was much less change in the depth of the chest. None of the measurements for girth or circumference show losses equal to the loss in weight, but some of them are not much less: waist, 19.6, thigh, 18.7 per cent. The Levanzin fasting data illustrate strikingly that circumferences as usually measured depend on present weight condition. Measurements of the bony width unfortunately were not made.

TABLE 2—*Physical Measurements at the Beginning and End of a Thirty-one Day Fast, Subject, Levanzin*

Name of Measurement	Just Prior to Fast	On 31st Day of Fast	Percentage Loss
Body weight	60.6	47.4	21.8
Height	170.7	170.7	0.0
Girth of waist	78.0	62.7	19.6
Chest girth (normal)	87.9	80.0	9.0
Circumference of thigh	48.8	39.6	18.7
Right biceps, flexed	27.9	23.9	14.3
Right forearm, extended	25.4	22.4	11.8
Right calf	33.5	30.0	10.4
Left calf	34.5	29.5	14.5
Depth of chest	25.4	22.9	9.8
Depth of abdomen	18.8	15.2	19.1

Another publication which has been issued by the Nutrition Laboratory gives the data on two groups of twelve men each whose diet was so restricted as to produce considerable change in body weight<sup>12</sup>. The twelve physically fit young men who made up Squad A lived for approximately four months on an energy intake of about 1,900 calories a day each, and thereby lost an average of 10.7 per cent in weight. The associated average changes in different circumferences were the following: axilla, 9, umbilicus, 6.9, nipples, 5.7, hips and buttocks, 4.6, and thigh, 8.3 per cent. The correlation between the percentage losses in weight and in girth at the umbilicus was  $0.76 \pm 0.082$ . Squad B was constituted of twelve men who took a more severe reduction in diet for a shorter period. As a result they lost, on the average 6.5 per cent of their former weight. The associated losses in girth were: axilla, 6.1, umbilicus, 5.1, nipples, 4.3, hips and buttocks, 4, and circumference of

11 The subject took absolutely no food during the thirty-one day period. The distilled water consumed each day varied from 720 to 900 cc. He even bathed in distilled water.

12 Benedict, Miles, Roth, and Smith. Human Vitality and Efficiency Under Prolonged Restricted Diet, Carnegie Inst. Wash. Pub. No. 280, Washington, 1919, p. 239, table 17.

thigh, 66 per cent. This last is noteworthy in being as great as for weight. All of these data from this "low-diet research" were made in connection with the taking of the DuBois measurements for determining body surface. They demonstrate the weight-circumference relationship stressed in the foregoing.

The largest and at the same time scientifically accurate mass of observations on physical modifications under inanition were reported on in 1923 by Professor Ivanovsky<sup>13</sup>. The report, which is edited by Dr. A. Hrdlicka, is based on the changes caused by famine in Russia. Observations by anthropologists were continued for three years at semi-annual intervals so that all subjects were measured six times. Presumably the data given represent the first and sixth measurements. The report is based on 1,248 men, their ages ranging from 25 to 55 years, and 830 women whose ages ranged from 20 to 55 years. The subjects belonged to several different ethnic groups. There is scant indication of the manner or conditions of the measurements or of the extent of the reduction in food. The data published cover the following points:

- 1 Loss in weight in percentage groups—1-10, 11-20, 21-30, and 31-40
- 2 Stature
- 3 Thoracic circumference in percentage of stature
- 4 Trunk length, jugular incisura to pubic symphysis, (with men only)
- 5 Length of arm in percentage of stature
- 6 Length of leg in percentage of stature
- 7 Length of head, vertex to chin
- 8 Horizontal circumference of head
- 9 Anteroposterior diameter of head
- 10 Transverse diameter of head

We have computed the losses for the different physical measures and give these percentages for men and women separately in table 3. It is not possible for us to secure from the Ivanovsky article a satisfactory value as a mean for loss in weight. He gives this only in terms of the percentage of persons falling within certain ranges of loss in weight. Probably the average reduction in weight was 15 or 16 per cent. Among those examined, every person decreased in weight, and this decrease was the noteworthy change as a result of the famine. The decrease was rapid within the first month, and weight reached its lowest point in the third or rarely the fourth half year of the famine. There were only slight changes in weight later, even though the amount of food was somewhat increased. The percentage decrease for obese persons was greater than for thin people, and in general, the decrease was more rapid and reached its lowest point more quickly in women than in men. Ivanovsky describes weight in man as the character which shows "most frequent and greatest variation," and he states that it is more variable

<sup>13</sup> Ivanovsky, Alexis. *Physical Modifications of the Population of Russia Under Famine*, (Translated by W. Jochelson and edited by A. Hrdlicka) *Am. J. Phys. Anthropol.* 6:331, 1923.

among civilized people than among uncultured tribes. The table shows slight losses, less than 1 per cent, in length of the arm and leg. The decrease in stature is unprecedented. A shrinkage of 46 mm for the men and 39 mm for the women seems remarkable, especially when we refer to the Levanzin data. Ivanovsky does not appear to be much surprised at the change in stature. He notes that army recruits have reduced the stature temporarily from 30 to 50 mm by standing, walking and bearing heavy burdens. The thoracic circumference was reduced 7.2 per cent for men. This was about the same ratio to the change in weight as occurred in Levanzin. The diameters of the head, even though practically bony measures, give definite decreases. A change of 4 per cent in the transverse diameter means a reduction of 6 mm for

TABLE 3—*The Ivanovsky Data for the Influence of Famine on Physical Measurements of Men and Women in Russia*

Name of Measurement		Men, Percentage of Loss	Women Percentage of Loss
1	Weight	15.9*	15.2*
2	Stature	2.8	2.5
3	Thoracic circumference	7.2	†
4	Length of trunk	6.2	†
5	Length of arm	0.7	0.3
6	Length of leg	0.6	0.0
7	Length of head	4.1	4.3
8	Circumference of head	3.7	3.4
9	Head diameter anteroposterior	2.2	1.7
10	Head diameter transverse	3.9	4.0
Weight ‡			
	1 to 10	23	32
	11 to 20	49	50
	21 to 30	21	15
	31 to 40	1	0

\* An approximation from the data as published.

† No data are given for the women.

‡ Different ranges for percentage of loss of weight, for example 49 per cent of the men lost from 11 to 20 per cent in body weight.

both men and women. We can but regret that it was not practicable to make any pelvic or other body width measurements. These data show, in general, that weight is the least stable measure, thoracic circumference is next, and length, particularly of the extremities, is the most stable. Even bony measurements change appreciably under a long period of famine.

#### BODY MEASUREMENTS DURING RAPID GAIN IN WEIGHT AFTER THYROIDECTOMY

Our own data concern gains in weight shown by adults following operative treatment of hyperthyroidism. These measurements were made in the thyroid clinic at the New England Deaconess Hospital in Boston by permission of Dr. F. H. Lahey. No selection was exercised except that the patients all had had high basal metabolic rates before operation. The patients were measured carefully by one of us (H. F. R.) a day or so before operation and also when tests for

metabolism were made. About six months following thyroidectomy, they were again measured in the same manner and by the same person. The two sets of measurements are directly comparable.

(a) *Methods*—The particular group of physical measurements employed did not concentrate on circumferences as is ordinarily done, but placed more stress on body widths. Each measurement was chosen with the following considerations in mind: (1) practical applicability for both men and women, (2) its recognition as a standard measure familiar to physical anthropometry, (3) the relative accuracy with which the measure could be taken promptly, and (4) skeletal measurements in which the calipers when applied would be against bony resistance. The measurements and procedures in most instances followed the recommendations of Hrdlicka<sup>14</sup>. Each patient wore a hospital nightgown, the weight of which was deducted, so that the results given for body weight are net and represent the weight taken during a fasting condition.

Height was taken with the subject standing erect, with heels, buttocks, shoulders and head applied against a vertical wall to which the centimeter scale was attached. The visual axis was horizontal. With the subject standing in the same position, the height to the suprasternal notch was measured by projection with the use of a level and a plumb bob (Hrdlicka, pages 66-67). The stem length, ordinarily termed "sitting height," was taken after the manner of Dreyer<sup>15</sup> with the subject seated on a level floor, the knees flexed, special care having been taken that the sacral region was well applied to the vertical. Taken in this manner, the measurement is free from interference by the voluntary contraction and the thickness of the gluteal muscles. The three measures of length—stature, sternal notch and stem length—were taken by using the simple double meter-stick and triangle device which we have described elsewhere<sup>16</sup>. The span of the olecranon, total distance from tip to tip of elbows, forearms flexed, has been used little if at all by anthropometrists. It has the practical advantage of bony terminals, and when thus flexed, the subject cannot voluntarily modify the shoulder girdle to the same extent through stretching that he can in the ordinary span measurement. The span of the olecranon was taken with the subject flat against the wall with one elbow applied to the adjoining wall.

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14 Hrdlicka, A. *Anthropometry*, The Wistar Institute of Anatomy and Biology, Philadelphia, 1920.

15 Dreyer, G., and Hanson, G. F. *The Assessment of Physical Fitness*, London, 1920, p. 5.

16 Miles, W. R., and Root, H. F. *A Simplified and Trustworthy Means of Measuring Stature*, Boston M. & S. J. **192** 111-112, 1925.

In measuring diameters of body width, we did not use the straight arm sliding caliper ordinarily employed in anthropometry, but rather the large curved caliper of the obstetrician. This had rounded points which can be pressed well in against bony resistance, and which can be read at the moment. The acromion measure for shoulder breadth was the caliper distance between the superior external borders of the acromion processes. The pelvic transverse diameter used was the maximal distance between the external margins of the iliac crests. The depth of the chest was taken as the horizontal distance from the lower end of the sternum to the posterior vertebral process of the corresponding level. The diameter of the bony transverse chest was measured at the level of the xiphoid process. Girth of the chest was measured at the level of the nipples and was the median of the subject's natural inspiration and expiration girths. Such a series of measurements is not difficult to take and requires not more than ten or fifteen minutes when the subject is ready.

(b) *Results*—Data for fourteen patients, eleven women and three men, are summarized in table 4. The range in age was from 23 to 61 years. Many other patients were given the preliminary measurements, but it was not possible to secure the second set. We are aware that the group is small, but, considering the extreme paucity of data on this general problem, our observations perhaps have an interest out of proportion to the size of the group examined. Ordinarily it is not good practice to include women and men in the same physical average, but careful scrutiny of the results fails to reveal any injustice from considering them all as one group. The presentation in table 4 is fairly self explanatory. Weight is given in terms of kilograms, while the other physical measures are given in centimeters. The mean preliminary weight was 53.3 as compared to 62.4 kilograms approximately six months after treatment. Every patient showed an increase in weight. The increases ranged from 4 to 14, averaging 9.1 kilograms, which represents a change of 17.1 per cent with the earlier weight as the base. The period between the two series of measurements as stated in the table was approximately six months, actually, it averages one hundred and ninety-five days. The shortest interval which elapsed between the two series of measurements was one hundred and sixteen days, the subject was a woman. During this period she gained 7.7 kilograms, or 14.7 per cent. The longest time which elapsed between series was two hundred and ninety-three days, this subject, a woman, gained 7.9 kilograms, an increase of 13.2 per cent. The extreme gains in weight were those of a man showing 26.1 per cent (13.7 kilograms) and of a

woman with a gain of 25 per cent, an increase in weight of 11.9 kilograms. The smallest gain was that of a woman, who in an interval of one hundred and ninety-four days gained 4.4 kilograms, equaling 9.3 per cent. The percentage of the loss in body weight for this hyperthyroid group is about the same as the loss for the Russian group and not quite so large as the loss in the case of the thirty-one day fast.

The results for body length in general indicate but slight change. Height increased 0.1 per cent, sternal notch height 0.2 per cent and stem length 0.4. In all three of these measures there were subjects who did not show a gain but rather a slight loss. The losses were always less than 1 cm., and the gains were usually less than 1.5 cm.<sup>17</sup>

TABLE 4—Physical Measurements in Patients with Hyperthyroidism Before and After Operation

Part Measured*	Average Observed Values		Direction and Amount of Change Exhibited				
	Just Prior to Operation	Six Months After Operation	Number of Cases		Range of Difference	Average Difference	Per Cent Difference
			Plus	Minus			
Body weight	53.3	62.4	14—		+14 to +4	+9.1	+17.1
Height	162.8	162.9	9—	7—	+1.5 to -0.8	+0.1	+0.1
Sternal notch	132.6	132.9	10—	3†	-1.1 to -0.4	+0.3	+0.2
Stem length‡	85.7	86.0	8±	6—	+2.2 to -0.9	+0.3	+0.4
Span olecranon	86.1	86.0	5—	8†	+1.6 to -2.0	-0.1	-0.1
Shoulders, acromion	34.2	35.0	10—	4—	+3.0 to -0.7	+0.8	+2.3
Iliac, maximal diameter	29.3	29.4	9—	5—	+0.4 to -0.3	+0.1	+0.5
Depth of chest	18.8	19.6	11—	3—	+2.0 to -0.3	+0.8	+4.2
Transverse diameter of chest	23.9	24.6	10—	4—	+2.7 to -0.5	+0.7	+2.7
Girth of chest	73.3	79.7	14—		+2.1 to +1.0	+6.4	+8.8
Basal metabolism, calories per Kg	38.2	23.9		14—	-5 to -23	-14.3	-37.1

\* All in centimeters except that body weight is in kilograms.

† Measurement missing in one subject.

‡ Taken in the manner prescribed by Dreyer.

The span of the olecranon was the only one of our anthropometric measurements that gave an average decrease, and this was slight, being only 0.1 per cent. Eight patients, however, showed decreases and five increases, the range was from +1.6 to -2.0 cm. The change probably came through a shift in the position of the shoulder blades.

There were four standard measures for body width. There was an average increase of 2.3 per cent in shoulder breadth, which in terms of the measurement is 8 mm. Shoulder width increased in ten of the subjects, in one as much as 30 mm, i. e., 7.5 per cent. This man had gained 19.9 kilograms. Decreases in shoulder width were slight, in two sub-

17 One patient showed a gain of 2.2 cm. in stem length. This is so far out of line with the plus values given by other subjects for the stem length that it seems probable that the base of the spine was not pressed back against the vertical in the preoperation measurement.

jects this width decreased 2 mm in each, in two others, 5 and 7 mm. The average iliac diameter before operation was 29.3 and after treatment, 29.4 cm. This diameter increased in nine subjects and decreased in five, but the total range covered was only 7 mm. eleven women show a measurement range of 27.2 to 32.8 mm in the iliac diameters following treatment. The latter figure is the measurement found for the heaviest member of the group, 66.8 kilograms. A woman with an iliac diameter of 27.7 was the lightest, 54.8 kilograms. The one in whom this diameter was 27.2 had a postoperation weight of 57.7 kilograms, but she was not the shortest of the women. On an average, the change in weight occasioned a shift of only 0.5 per cent in the iliac diameter. The depth of the chest shows a somewhat larger percentage of increase than does the transverse diameter of the chest, 4.2 as against 2.7 per cent. A definite majority of the patients showed an increase in each measurement. The range of increase was larger for the transverse diameter. In millimeters, the average change was almost the same for both diameters of the chest.

Increase in the girth of the chest taken at the level of the nipples was the invariable result when the weight had increased. This definite change in the circumference was from 1 to 21 cm., on the average it was 6.4 cm., which amounts to 8.8 per cent. This value compares fairly well with the 7.2 per cent found for Russian men and also with the 9 per cent found for the fasting man. Judging from the data on Levanzin (table 2) and that accumulated on Squads A and B in the low diet experiments, the girth at the level of the nipples is not as much disturbed by loss in weight as is the circumference at the axilla or at the umbilicus. Nevertheless, this measure is in a class by itself so far as amount of change is concerned when compared with body length or diameters.

Circumferences, in general, reveal more definitely the build of the body than does stature, as Davenport urges in his monograph on body-build and its inheritance<sup>18</sup>. The circumferences reflect also the present weight status or nutritional condition of the person in a marked degree. The native and more inherent body-build characteristics, as seen from the data presented, are revealed in the skeletal widths, which can be so taken as to escape in large part interference from any present overweight or underweight condition.

#### CONCLUSIONS

The group of data presented in this paper mutually supplement each other and lead to the following statements:

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<sup>18</sup> Davenport, C. B. *Body-Build and Its Inheritance*, Carnegie, Inst. of Wash. Pub. No. 329, Washington, 1923.

1 Body weight in adults is normally the measure showing the largest variability, while stature is the least variable of the ordinary physical measurements. Stature is, therefore, not the best basis from which to estimate normal weight.

2 In adults who have shown marked changes in weight through fasting or decreased intake or as a result of thyroidectomy (new data), changes in circumferences and girths parallel closely changes in weight, and hence are ruled out as a basis for weight prediction.

3 Certain bony body widths, which have a natural variability about midway between stature and body weight, are found to change but little when persons lose or gain as much as from 15 to 20 per cent in weight. These width diameters, notably the intercrestal iliac diameter, are important in determining body-build and should receive due emphasis in tables on normal weight.

# ANTITHROMBIN TEST IN TYPHOID FEVER

## IMPROVEMENTS IN TECHNIC <sup>1</sup>

C A MILLS M D

PEKING, CHINA

Kitzmiller and I have certain new developments in technic to offer those who may be interested in our antithrombin test previously described <sup>1</sup>. These are, first, the use of purified fibrinogen and thrombin solutions instead of citrated horse plasma and serum, second, the adaptation of the method to from 0.1 to 0.2 cc of the patient's serum so that venipuncture may be dispensed with, and, third, such simplification of the method that laboratory technicians anywhere may perform it, without possessing special knowledge of blood clotting.

The first alteration in technic, the use of purified fibrinogen and thrombin solutions, was prompted by the discovery that repeated bleedings of an animal to obtain the citrated plasma needed caused the development of such an excess of antithrombin in the animal's blood as to render it an unfit medium for detecting an excess of this element in a patient's blood. By the use of the purified thrombin and fibrinogen solutions described below, almost all the antithrombin of the horse plasma is eliminated, and in this way one of the most troublesome variables of the method is avoided. The second change, the use of 0.1 or 0.2 cc of the patient's serum, is of particular value in China, where venipuncture is dreaded by the people, but a finger prick is accepted stoically at any time. By using the bent Wright tubes of about 0.5 cc capacity, one may easily obtain sufficient blood from the patient's finger or ear. The use of serum instead of citrated plasma allows the choice of this method of drawing the blood. The third improvement consists in the taking of only a single reading of the thrombin activity of the mixtures at the end of two hours, instead of the repeated readings previously advised. This is made possible by the use of the purified solutions and the elimination of the antithrombin variable of the citrated test plasma.

## PREPARATION OF SOLUTIONS

The following solutions are prepared and kept on ice.

1 *Blood Fibrinogen*—Blood of any mammal (we use the horse) is drawn into a vessel containing sufficient sodium citrate to give a final concentration of 0.5 per cent, the blood being well stirred to provide prompt mixing. The plasma is collected by centrifugalization. To 25 cc of plasma are added 4 Gm sodium chloride. The precipitated fibrinogen is collected and washed several times in

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<sup>1</sup> From the Department of Medicine, Peking Union Medical College.

1 Mills, C A, and Kitzmiller, K V. Aid in the Diagnosis of Thyroid Fever. A New Laboratory Method, Arch Int Med 38:544 (Oct) 1926.

15 per cent sodium chloride solution containing 0.5 per cent sodium citrate. It is finally dissolved in 25 cc of 0.5 per cent sodium citrate solution, and in this form will keep several days in the icebox.

2 *Thrombin*—To the 25 cc of plasma from which the fibrinogen has been removed in the foregoing, as described, 9 Gm of ammonium sulphate are added, and the precipitate collected on a filter. It is allowed to drain thoroughly on the filter and finally all sulphate solution possible is pressed out between layers of filter paper. This obviates the necessity of dialyzing out the ammonium sulphate. This precipitate contains practically all the prothrombin of the plasma. It may be bottled as the moist paste, and in this form it will keep for weeks. When desired for use, 0.25 Gm is dissolved in 10 cc of water, and to this solution are added 2 cc of a 0.1 per cent emulsion of cephalin and 2 cc of 1 per cent calcium chloride solution. After this mixture is allowed to stand at room temperature for thirty minutes to get a maximum thrombin production, it is ready for use. It will then hold practically a constant thrombin activity for several hours, but should not be used on a succeeding day.

#### METHOD OF TEST

The actual procedure of the test now is as follows. Blood is obtained by a finger prick drawn into a Wright tube, allowed to clot and the serum squeezed out, or the clot is broken up and centrifugalized down. The serum is drawn off through a capillary pipet, and 0.1 or 0.2 cc is measured into a small test tube and heated in a water bath to 60 C for ten minutes. Five or six serums may be tested in one series just as easily as a single specimen. Along with the patients' serums a similar procedure must always be performed on the fresh serum of a healthy person (I use my own blood drawn in the fashion described in the foregoing). The heated serums are now cooled, and to each tube is added three times as much thrombin solution as there was serum originally taken. If 0.1 cc serum is taken, then 0.3 cc thrombin solution is added to that tube. In addition, one tube of 0.9 per cent sodium chloride solution as a control is prepared in a similar fashion. The thrombin solution here used should be prepared as directed in the foregoing at least thirty minutes before it is to be used.

This series of tubes is set aside at room temperature for two hours, and at the end of this time 0.2 cc of each mixture is added to 0.25 cc of the fibrinogen solution in a water bath at from 38 to 40 C, and the time required for clotting of the fibrinogen is noted. The saline control will probably clot the fibrinogen in about thirty seconds, the control serum tube in from four to six minutes and any typhoid serum tube in double the time required by the control serum. The tubes should not be shaken, but should be inclined gently to note clot formation.

Precautions in handling typhoid serum to prevent infection in the technicians is necessary only up to the time of heating the serum, as the heating to 60 C for ten minutes minimizes the risk. Kitzmiller and I, however, always insist that laboratory technicians and assistants who handle the blood of patients should be given the regular course of typhoid vaccine.

When we have reduced the antithrombin method to a more satisfactory and exact form, we hope to submit some interesting data as to its significance in the near future. Typhoid fever is prevalent at all times in Peking. Our work here so far has drawn a sharp line of distinction between typhus and typhoid, the former never exhibiting a considerable increase in antithrombin. This point is of great value, since the two fevers are so similar during the early part of their course, when both Weil-Felix and Widal reactions are negative.

# PRESENT STATUS OF CURABILITY OF BRONCHIAL ASTHMA

WITH REPLIES TO A QUESTIONNAIRE <sup>1</sup>

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NEW YORK

Reports of the benefit derived from the methods of treatment of bronchial asthma are extremely diverse and often depend on the enthusiastic preconceptions of the physician, the psychic susceptibilities of the patient and the spontaneous tendency of the disease to remissions, aggravations and improvement.

In the earlier work on anaphylaxis and protein sensitization, the parallel symptoms suggested asthma to be a phenomenon of anaphylaxis <sup>1</sup>. According to this view, a person who has asthma is sensitized to a definite substance, and an attack occurs every time this substance enters the circulation. In the actual processes which take place in nature, the effective doses may be infinitely small, and it may well be possible that the minute quantities contained in the emanations from horses, cats or guinea-pigs are sufficient to act as a toxic dose and cause the nonfatal stenosis of the bronchi evidently present in an asthmatic attack in man. Perhaps certain digestion products of the proteins now and then become absorbed into the circulation from the alimentary canal, in some cases in an abnormal stage. The following parallel facts may be recalled: (1) the sensitization to anaphylaxis may be hereditary or acquired, (2) anaphylaxis is specific, (3) animals sensitized to a definite protein can be intoxicated only by that protein, and (4) atropine which relieved asthma, relieved also the anaphylactic attack, as discovered by Auer and Lewis <sup>2</sup>.

Sensitization tests have been held to indicate protein intoxication. The first sensitizing dose of egg white injected into an animal is digested, but the process goes on so slowly that no effect can be seen. An immediate effect on reinjection, especially a fatal issue, depends on the rapidity with which the protein is split up and its poisonous constituent set free <sup>3</sup>.

Manwaring believes that increased specific capillary permeability will ultimately be shown to be the dominant fundamental physiologic change

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\* From the Department of Cardiovascular Diseases, Beth Israel Hospital

1 Meltzer: Bronchial Asthma as a Phenomenon of Anaphylaxis, J. A. M. A. **55** 1022 (Sept. 17) 1910

2 Auer and Lewis: J. Exper. Med. **12** 151, 1910

3 Vaughan: Am. J. Med. Sc. **145** 161 (Feb.) 1913

in protein sensitization, to which all other anaphylactic reactions are secondary <sup>4</sup>

The brilliant work of Weil is most significant as having shown that the anaphylactic reaction is cellular <sup>5</sup> Immune bodies in the blood do not contribute in the slightest degree to its production

Experimental anaphylaxis, on the one hand, and such diseases as asthma, hay-fever and urticaria, on the other have another feature in common They are all associated with an eosinophilia Moschcowitz considered the invasion of eosinophils in increased numbers into the organism as the expression of an active agent or the agent itself in the production of anaphylaxis <sup>6</sup> This is further emphasized by the fact that through continued parenteral administration of foreign protein, a peripheral blood eosinophilia may be produced in animals Following recovery from anaphylactic shock, an intense eosinophilia likewise occurs, and the lung tissue exhibits a marked eosinophilic infiltration, with a peribronchial collection of these cells Similar changes may be produced by inhalation of serum in animals sensitized intraperitoneally In Arthus's skin phenomenon, the cells of the inflammatory swellings are chiefly eosinophils A local eosinophilia of the submucosa is seen in the gut of dogs following anaphylactic enteritis It is possible that certain products are formed in parenteral administration of protein which exert a positive chemotactic action on eosinophils, they are attracted from the blood and bone marrow in which they are present in increased numbers <sup>7</sup>

As shown by the data in this article, as well as by the work of a number of authors, anaphylaxis may be dismissed from consideration in this disease Anaphylaxis is an induced hypersensitiveness caused by the presence of specific antibodies in certain tissues The symptoms of anaphylaxis are caused by the meeting of these antibodies with the respective antigen in those tissues It has been shown to be non-inheritable in the biologic sense It seems necessary to conclude, first, that if anaphylaxis does occur in man, it does so rarely, and second, that there is not any positive evidence that anaphylaxis occurs in human beings <sup>8</sup>

Concerning hay-fever, Cooke indirectly suggests that it may be a manifestation of an idiosyncrasy to ragweed similar to the idiosyncrasy to drugs such as quinine and acetylsalicylic acid, and that it may not have anything to do with anaphylaxis <sup>9</sup> Again, it seems hardly correct to class hay-fever or asthma with the typical anaphylaxis seen in the

4 Manwaring Capillary Permeability in Anaphylaxis, *J A M A* **80** 303 (Feb 3) 1923

5 Weil *J M Research* **30** 87 1914

6 Moschcowitz, Eli *New York M J* **93** 15, 1911

7 Schlecht and Schwenker *Deutsche Arch f klin Med* **108** 405, 1912

8 Coca *J Immunol* **5** 363 (July) 1920

9 Cooke Allergy in Drug Idiosyncrasy, *J A M A* **73** 759 (Sept 6) 1919

artificial sensitization of animals and man, because the principles of anti-anaphylaxis do not apply. Thus, active sensitization of guinea-pigs to ragweed pollen extract apparently is impossible<sup>10</sup>. Attempts to transfer antibodies from man to animals as well as the demonstration of circulating antibodies to ragweed in a test tube is at best variable. In active anaphylaxis the presence of circulating antibodies is one of the striking features, whereas in ragweed hay-fever, the presence of circulating antibodies is vague and doubtful<sup>11</sup>. Koessler<sup>12</sup> and Clowes<sup>13</sup> found that circulating antibodies decrease rather than increase as the process of immunity progresses. Yet the treatment with pollen substances for the purpose of immunization is still used, and an attempt is not made to arrive at a more basic cause for the asthma.

#### HEMOCLASIC REACTION AND VAGOTONIA

The path of study opens again into wider channels with the studies of Widal and his co-workers<sup>14</sup>. They attribute anaphylactic reactions and idiosyncrasy to a constitutional predisposition in which the person reacts with flocculation of the colloids in the blood serum, the so-called hemoclastic or colloidoclastic reaction. As part of this reaction, there is a sudden fall in the total number of leukocytes in the circulating blood. Thus in one patient, exposure to pollens, antipyrine or acetylsalicylic acid induced immediate hemoclasia, with a drop in the leukocytes, generalized eruption, sneezing and an attack of asthma. Chilling of the skin on stepping out of a warm bath was enough to bring on all the symptoms. This suggests that while anaphylaxis may be the cause of some of the manifestations, others must be ascribed to an idiosyncrasy, which proves that the underlying cause of both is the instability of the colloidal balance in the plasma.

That asthma is a manifestation of overexcitability of the pneumogastric system, has long been surmised<sup>15</sup>.

It is obvious that there is not a single cause, but that several factors, internal and external, combine in varying proportions in the clinical picture. Vagotonia is an indispensable element, but inadequate alone to induce asthma. Colloidoclasia is probably an effect, not a cause. These two elements recall the neurosis and the dyscrasia of the old school. Thus our predecessors, with clinical observation alone, recognized the main elements of the problem. The final solution must be sought in

10 Cooke, Flood and Coca. *J Immunol* **2** 217 (Feb.) 1917

11 Besredka in Krauss u. Levaditi Handb. etc. *Erganzungsbl.*, I, p. 246

12 Koessler in Forchheimer *Therapeutics of Internal Diseases*, ed. 5, New York, D. Appleton & Co., 1914, p. 671

13 Clowes. *Proc. Soc. Exptl. Biol. & Med.* **10** 69, 1913

14 Widal, Abram and Lermoyez. *Presse med.* **30** 189 (March 4) 1922

15 Eppinger and Hess. *Vagotonia, Nerv. & Ment. Dis.*, Monograph Series, New York, 1917

biology and probably in physical chemistry, and, most important, in the phenomena of heredity<sup>16</sup>

#### IMMUNITY AND DESENSITIZATION

The reports in the literature of spontaneous immunity in cases of protein sensitiveness are not a pledge for permanence of immunity. Thus Schloss studied eight infants affected with idiosyncrasy to egg<sup>17</sup>. The patients developed urticaria from one to three hours after the egg was ingested. Desensitization always occurred after the development of toxic symptoms and lasted for a period of from thirty-three to forty-five days. During this time, egg white could be ingested without harmful effect, and the cutaneous test to egg protein was negative. The cutaneous test to egg protein and the development of toxic symptoms after the ingestion of egg white were in close accord.

Contradictory opinions are entertained regarding the amount of antigen to be used in therapeutic prophylaxis. Sewall, from carefully conducted experiments on guinea-pigs, emphasized that small instillations of serum have a positive inhibiting effect over the development of anaphylaxis, but that hypersensitiveness is maintained by repeated application of the larger dosage<sup>18</sup>. He concludes that clinically better results may be expected by choosing a dosage of antigen which fails to produce an obvious reaction than by one which entails a marked disorder. After the use of vaccines clinically in a series of cases, Rackemann, on the contrary, concluded that good results occurred only in those cases in which the various doses of the vaccine are followed by local reactions at the site of inoculation<sup>19</sup>.

The confusion which exists is further indicated by Vaughan who states

If we may assume, from our meager knowledge of the immunology of this disease, that relief of symptoms following preventive inoculation is due to an increased tolerance (as in morphinism) rather than a true immunization, and that the condition resulting is one of so-called antianaphylaxis, the daily administration of small amounts would appear to be a more logical procedure than the giving of larger amounts at much longer intervals<sup>20</sup>.

The use of nonspecific proteins is exploited on the basis of beneficial clinical results. A nonspecific element enters largely into the benefits derived from specific desensitization. Milk has been used as a non-

16 Segard *Rev de med* **38** 457 (Sept-Oct) 1921

17 Schloss *Desensitization in Cases of Food Idiosyncrasy*, *J A M A* **73** 785 (Sept 6) 1919, *Proc Am Soc for Clin Investigation*, 1919

18 Sewall *J Lab & Clin Med* **2** 874 (Sept) 1917

19 Rackemann *J Immunol* **8** 295 (July) 1923

20 Vaughan *Specific Treatment of Hay-Fever During the Attack* *J A M A* **80** 245 (Jan 27) 1923

specific agent of choice because of its ready supply and ease of production <sup>21</sup>

It is evident that attempts at immunization have proved disappointing. The use of vaccines in this disease is entirely empiric, and their administration is not even in accord with the principles of vaccine therapy. Thus Rackemann and Thomas have the impression that prolonged use of vaccine appears to prevent relapses <sup>22</sup>. Such an observation is beset with fallacies in a disease so changeful as bronchial asthma <sup>23</sup>.

The need of apology for the use of vaccines in asthma is avowed in the following statement: "Although good proof of a cure brought about by vaccine is lacking, vaccines do good in many cases, and at least until we know more of the fundamental pathologic physiology of asthma, their use is reasonably justifiable" <sup>19</sup>.

Again, Davidson asserts that complete desensitization in man cannot be obtained. The phenomenon of lessened sensitiveness produced by injections of protein extracts in cases of hypersensitiveness has been called hyposensitization. Most patients are obliged to take treatment every year, as the hyposensitization is temporary. In a few cases, it has been known to last three years after one series of injections <sup>24</sup>.

In a group of ninety patients treated with autogenous vaccine by Hutcheson and Budd, the longest duration of complete relief was three years <sup>25</sup>.

In five cases of Lord's series, there was complete freedom lasting from one to five years, with recurrence after this interval <sup>23</sup>. This may be due to avoidance of exciting causes or to spontaneous remission.

Making the necessary allowance, the following is perhaps in accord with more general experience in vaccine treatment: "Of the entire series of 131 patients, 7 per cent have been cured, 22 per cent have been definitely benefited, 10 per cent have been helped somewhat, 18.5 per cent have been relieved temporarily but 41 per cent have not been relieved at all" <sup>19</sup>.

In one article, contradictory conclusions are expressed together with a mature skepticism.

In a certain relatively small number of cases, especially in children, the tests are of greatest value in demonstrating the cause of symptoms, and in most of these cases treatment, by avoiding the corresponding food, gives remarkable results. Subsequent study showed moreover, that in only about 13 of 100 cases was the finding of the test to food or animal protein really important and of use in further treatment. This figure is very small, but, as

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21 Schiff. *Am J M Sc* **166** 664 (Nov) 1923

22 Thomas. *Treatment of Asthma with Autogenous Vaccines*, *Arch Int Med* **34** 79 (July) 1924

23 Lord. *Diseases of the Bronchi, Lungs and Pleura*, Philadelphia, Lea & Febiger, 1925

24 Davidson. *J S Carolina M A* **19** 377 (Jan) 1923

25 Hutcheson and Budd. *Virginia M Monthly* **46**:218 (Feb) 1920

a matter of fact, the ability to really help a small number of patients undoubtedly justifies the great amount of routine work on many patients. Emphasis should be placed on the necessity of a fairly gross interpretation of any positive test. Too delicate or fine a reading merely clouds the picture and in addition renders further progress in this already obscure branch of science even more difficult.<sup>27</sup>

This profusion of articles has added voluminously to the literature on the subject, advancing the science of it but little.

#### THE NOSE AND BRONCHIAL ASTHMA

Voltolini's report of a cure following nasal operation was not substantiated by later observation.<sup>27</sup> Since then, however, nose specialists have done their share in the treatment of patients with bronchial asthma, but they have not been able to achieve a permanent cure in these cases.<sup>28</sup> It is gratifying to read the clear expression of Lord in his chapter on bronchial asthma on the relation between diseases of the nose and asthma. "It is sufficiently obvious that asthma is not always caused by nasal disease, and that nasal disease is more often unaccompanied by asthma than the contrary."<sup>23</sup> Nasal pirates alone (to use an expression of Dr. Max Kahn) proclaim their personal successes in this field, suggesting their own superiority in the treatment of these patients. It is becoming recognized that nasal operations are not of permanent avail in true bronchial asthma.<sup>29</sup>

Analyses of series of cases have shown that operations on the nose in the treatment of bronchial asthma are ineffective.<sup>30</sup>

#### METABOLISM IN ASTHMA

Regarding the metabolism of asthma, a number of careful studies have been made. Rosenbloom, in one case, found that the metabolism of nitrogen was normal, the urea, ammonia, creatinine, uric acid, amino acids, and undetermined nitrogen were normal in amount and in per cent of the total nitrogen. The sulphur metabolism was also normal. The total sulphate sulphur, inorganic sulphate sulphur, ethereal sulphate sulphur and neutral sulphur were also normal. There was a tendency for a loss of calcium in this patient. This was also true to a lesser degree regarding the magnesium and phosphorus. Rosenbloom surmised that the value of calcium in the treatment of bronchial asthma bears some relation to the loss of calcium in this condition.<sup>31</sup>

26 Rackemann. *Am J M Sc* **163** 87 (Jan.) 1922

27 Voltolini. *Proc Laryng Soc*, London, 1899, p. 83

28 Adam. *Asthma and Its Radical Treatment*, New York, Paul B. Hoeber, 1913

29 Krez. *Wurzb Abhandl u d Gesamtgeb d prakt Med* **14** 213, 1914

30 Walker. *Studies of the Cause and Treatment of Bronchial Asthma*, *J A M A* **69** 363 (Aug. 4) 1917. Kahn. *Nasal Operations in Bronchial Asthma*, *J A M A* **82** 536 (Feb. 16) 1924. Lintz. *Ann Surg* **79** 917 (June) 1924.

Heatley and Crowe. *Bull Johns Hopkins Hosp* **34** 410, 1923. Rowe. *The Treatment of Bronchial Asthma*, *J A M A* **84** 1902 (June 20) 1925.

31 Rosenbloom. *Interstate M J* **26** 174 (March) 1919

Kahn and Zugsmith, in a more general study of the metabolism, found that persons who have asthma suffer from a condition of tissue suboxidation. The neutral sulphur fraction increase showed this lack of oxidation. The creatinine output was low, thus indicating a lessened tissue oxidation.<sup>32</sup> Various other observers noticed a decrease of tissue oxidation in dyspneic animals.

#### "CURE" OF ASTHMA

In general, the implication of absolute cure or of permanence of results is too often made in the literature on bronchial asthma. Thus such statements occur as "A positive skin test is a necessary preliminary to successful specific treatment."<sup>33</sup> "Nearly 9 per cent of patients are entirely freed of their symptoms. These results were determined by a personal communication to each patient four to six weeks after the ragweed season",<sup>34</sup> and again, "the patients who gave a positive test to their own organism were treated with this organism, all of them with success." A subsequent paragraph in this paper qualifies, "The permanency of the favorable results obtained is as yet to be discovered, but most of these patients have retained, at least during the seven months of observation, the result which followed the treatment as given."<sup>35</sup>

I may say that since 1916, work has been done using autogenous defibrinated blood in the treatment of bronchial asthma.<sup>36</sup> In later reports, the results obtained were as favorable as those with any other method, such as vaccine, attempts at desensitization and even change of climate.<sup>37</sup> This method, therefore, far from being important as a measure of treatment, has the same value as any other method as far as the possibility of absolute cure of asthma is concerned.

Before the present methods of treatment were so generally utilized, equally "successful" results were recorded by Salter<sup>38</sup> in carefully studied cases observed over a long time. Thus, recording his remarks in different cases under the heading Effects of Remedies:

Principal remedy, smoking pure tobacco, attending strictly to diet, avoiding everything that disagrees, and choosing a locality that suits. Different rooms even make a difference to me. By these rules I have cured myself. Seven years ago tried Locock's wafers, and soon greatly improved. During the second year had but one attack, and that in a thunder storm. Since then, five years entirely free. Can do anything."

32 Kahn and Zugsmith. Metabolism of Asthma, Arch Int Med **21** 510 (April) 1918.

33 Rackemann. Bronchial Asthma Arch Int Med **22** 517 (Oct) 1918.

34 Rackemann. Boston M & S J **182** 295 (March 18) 1920.

35 Rackemann. J of Immunol **5** 376 (July) 1920.

36 Kahn and Emsheimer. Autogenous Defibrinated Blood in the Treatment of Bronchial Asthma, Arch Int Med **18** 445 (Oct) 1916.

37 Henske. J Missouri M A **18** 431 (Dec) 1921.

38 Salter. On Asthma. New York, William Wood & Co., 1882.

Apparently permanently cured himself by walking 20 miles a day  
Was prescribed a slight regular aloetic purge, tonics, an early dinner and nothing after it, plain, spare diet, avoidance of unwholesomes Cure complete

A blister or other counterirritant to the chest soon relieves A rhu-barb pill three times a week useful No attack for from six to eight months

Dietetic rules have given an almost perfect cure Pill contain-  
ing ext stramonium, grain  $\frac{1}{4}$ , hyoscin, grain  $1\frac{1}{2}$ , and conium, grain  $1\frac{1}{2}$ , com-  
pletely put a stop to the night paroxysms and cured the case Chloro-

form the only thing that has done good Morphia does harm Other remedies  
worthless Cured by London air Gin and water always cures

Coffee and emetics always relieve, niter-papers at first, hot spirits for a time  
Change of air to France always cures A mixture containing tincture

of opium, sulphuric ether and compound tincture of lavender cures like magic  
Cured by dieting Completely cured by leaving off meat at din-

ner Free purging and raw gin the only remedies Change from healthy  
to an unhealthy air has cured Joy's cigars do great good, an ordinary

cigar slight, emetics and stramonium temporary, coffee and chloric ether none  
India cures Cured by iodide of potassium Chloroform relieves, but

prostrates Niter-paper the only other remedy Iodide of potassium  
has cured Emetics always do good, niter-papers slightly Finally

cured by iodide of potassium

In my own experience, so inconstant are the results with various  
methods of treatment that I propose to patients the use of a number of  
methods at the same time, or one method following the other, while I  
hold the case under observation and further study These methods  
include the injection of autogenous sputum vaccine, the injection of a  
nonspecific protein, the treatment of any infectious foci such as sinuses,  
tonsils or teeth, antiasthmatic medication-epinephrine hydrochloride  
hypodermically for the attacks, potassium iodide as a thyreotropic  
sympathetic stimulant, belladonna as a vagus depressor, autogenous  
defibrinated blood and any other protein injection to which the patient's  
skin may react

It is evident that I do not decry the use of these measures if a better  
method cannot be found<sup>39</sup> I do not believe, however, that other phy-  
sicians who are doing the same thing and I am making efforts entirely  
in the right direction Physicians are led as much by any new measure,  
as if they did not conceive of the underlying basic phenomena that  
must be considered in bronchial asthma

#### ABSOLUTE CURE IN BRONCHIAL ASTHMA

In reply to an inquiry on the curability of bronchial asthma recently  
sent out to the workers most prominent in this field in the United States,  
replies with permission to publish them were obtained from those whose  
experience is most to be considered A few others regretted their  
inability to answer the queries on the ground that it would be giving  
their opinions to a profession not yet prepared to receive them Their

<sup>39</sup> Ortner Vorlesungen über Spezielle therapie Immer Krankheiten,  
Vienna, W Braunmuller, 1923

names are therefore considerably omitted from this article. The following are abstracts of the letters, I have taken great care to include in each the context so as to give their essence fully.

DR MARK J GOTTLIEB, New York. I can only say that in my experience, which runs over a period of twelve years, absolute and permanent cures of asthma were unobtainable.

I am in accord with most of the conscientious workers in this field when they say that the disposition to asthmatic attacks is inherent in the constitution of the individual when he or she is born, and that fundamental quality cannot be changed.

I have in my files a number of cases which I have followed for periods free from symptoms running from twelve to five years, but even these may from time to time have recurrences of their malady due to the acquisition of new respiratory infections, intestinal upsets or disturbances generally which cause a malfunction of elements which control the involuntary musculature of the body, particularly the muscles of the bronchi and bronchioles.

I have no objection to the use of my name under this statement, for I know that it summarizes as truthfully as is possible the facts as I find them.

DR GEORGE PINESS, Los Angeles. If I knew what you meant by an "absolute cure" of bronchial asthma I think I would be in a better position to answer your questionnaire, but since I do not know what it means, I cannot do so. In my experience of almost ten years in allergic work, during which time I have done nothing else, I have many patients who have been free over this period of time, others for a shorter period of time, but I cannot say offhand how many have been entirely free during the years they have been under my care. Personally, I do not believe that one can say that an asthmatic is ever permanently cured, because of the peculiar etiology which is so well known to you. I believe that the term "free from symptoms" should be used instead of "cured."

DR FRANCIS M RACKEMANN, Boston. I know that I have one or two absolute cures and it may be many more, because occasionally somebody comes in who tells me that they know of a former patient of mine, who, since taking treatment, has had no further asthma.

DR HENRY SEWALL, Denver. I can only say that this environment seems to be astonishingly remedial in certain typical cases in which the patient comes here from other climates, as Chicago, but I have seen considerable numbers of asthmatic sufferers who seemed as badly off here as elsewhere. The whole problem is most fascinating, and I know none whose consideration is more likely to be warped by mental preconceptions.

DR F W GAARDE, Rochester, Minn. Owing to the fact that our patients come, as a rule, from such great distances, and because of the difficulty in obtaining reliable reports in answer to letters of inquiry, I am unable to give you the information you ask concerning our results in asthma.

We can get a general idea as to the patient's condition, but to have a definite statement as to positive cures is too uncertain a thing to warrant placing in statistics. I am sure that you realize that we are situated differently from the physician who is in constant close touch with his patients.

DR ANDREW C HENSKE, St Louis. I suppose you have reference to the treatment with autogenous defibrinated blood. In the past ten years I have treated about thirty patients by this method. In this series there are only five patients to my knowledge who have remained absolutely free from symptoms for over a period of five years or more. Ten others derived temporary benefit, and the balance apparently no relief at all.

My experience with the protein sensitization tests and treatment after the method of I Chandler Walker has been unsatisfactory.

In fact, I have had few permanent results from any one method of treatment. On the whole would say that despite the optimistic reports found in

the current literature, the question of curative treatment of bronchial asthma is still an unsolved problem

DR CHARLES H EYERMANN, St Louis One can interpret the term cure in two ways, first, symptomatic cure and second, disappearance of positive skin tests

I will answer the second question first by saying that I do not recall a case in which the skin tests disappear despite absence of symptoms, whether as the result of treatment or mere avoidance of contact However, positive skin reactions do disappear as exemplified by a lad of 13, who has had the classical sequence of eczema, urticaria and asthma, who as an infant gave unmistakable positive reactions to egg white He now gives no reaction to egg white, but reacts to many other substances, and he still has eczema, hay-fever and asthma

I have had several asthmatic patients under observation for a number of years, the longest since 1919, who have remained symptom-free as long as they have avoided the offending protein None of these patients have had specific treatment, all have taken care of themselves by avoiding contact One of these, just recently had an attack of asthma by the ingestion of the offending protein, wheat A second one, whose condition was also caused by wheat, is now able to eat wheat apparently in any quantity without having asthmatic attacks However, inhalation of flour dust produces vasomotor rhinitis and, if in sufficient concentration, asthma ensues I have not treated asthmatic patients with specific substances when it has been possible for them to avoid these substances, which has been the case in the majority of instances Such patients consider themselves cured, because they can control their symptoms or be free from asthmatic attacks by avoiding contact, although from an immunologic point of view, they are not cured I have observed two cases of a definite bronchospasm, not giving positive cutaneous reactions, in which the patients have remained free from their asthmatic attacks for a period of two years, while tuberculin was being administered These patients are still being treated with an occasional injection of tuberculin These certainly are cured from the patient's standpoint I cannot say definitely whether they are or not

I have also had experience in observing persons with seasonal asthma in whom, following preseasonal and proseasonal pollen injections, there have been no asthmatic attacks They have also continued having hay-fever symptoms of greater or less degree Again, a cure from the standpoint of the patient

I cannot give the percentages of cures as judged by the foregoing, for I have not compiled all the cases that I have seen

DR F M POTTENGER, Los Angeles I cannot give you any information as to the absolute cure of asthma It is only recently that I have taken into my institution any patients suffering from asthma, who did not have complicating tuberculosis, so I cannot give you a large series under any circumstances I have found that by the methods we use, we have been able to relieve about 50 per cent of the patients This is simply a rough estimate

DR I CHANDLER WALKER, Boston I cannot give you absolute statistics regarding cures of asthmatic persons Some marry and change their names and address, many move and some do not answer questionnaires Therefore, it is impossible to follow many patients

In my office, I feel sure more than 75 per cent of persons with vaccine cases have their asthma stopped for the remainder of the winter Many, however, have to be treated the next fall in order to be free for the succeeding winter I do not know how many are cured for years, but every week I usually hear of from three to four old cases that I treated with vaccine three or four or five years ago, and these have been free from asthma ever since, so that I get considerable encouragement that many asthmatics are cured for several years at least by one or two courses of vaccine I have many patients with pollen cases who have remained free from asthma for two, three, four, or five years, following two or three years preseasonal pollen treatment, but I could not

possibly tell the percentage Failures, however, are rare for the season immediately following a course of treatment

Failures in food sensitive and animal sensitive cases are rare, and I do not know of more than two or three such cases in which there has ever been a relapse, and these few have become bacterial cases and the patients have been cured by vaccine treatment

DR ALBERT VANDER VEER, JR, New York I am very sorry, but I do not think we can give you any definite figures which would be of any value on the absolute cure of bronchial asthma We avoid the term intentionally, substituting the words "relief of symptoms," and even using this terminology, it is difficult to state in percentages what our results are With the asthma cases due to pollen it is of course comparatively easy because if the patient is free during his season, under treatment, and exposed, we may consider him relieved of symptoms and the percentage in these cases is about 80 Patients sensitive to animal epithelia are of course free from asthma as long as they are not exposed to the animals in question Patients who have had horse asthma whom we have treated, almost invariably do well, and as a guess, I should say that the percentage of freedom from symptoms was between 80 and 90, but this is only a guess Patients with asthma due to chronic sinus infection are, of course, the most difficult to treat, and while in the majority the condition clears up under treatment, they are likely to have a recurrence

DR W W DUKE, Kansas City Success in treating asthma depends, of course, on the cause Of pollen cases, last year I cured 100 per cent of patients in which the condition was not complicated with sensitiveness to heat or cold A small number of pollen cases are complicated by this condition, and in this case are more difficult to get rid of symptoms completely Furthermore, symptoms are inclined to continue during the winter months when this is the case Of perennial cases and seasonal cases caused by sensitiveness to cold, I think all patients were made symptom-free with relatively simple measures

Of the patients sensitive to heat, I think we relieved a little more than 50 per cent In cases of combined sensitiveness to heat and cold, we were perhaps less fortunate, but this does not include a large per cent of cases as they come to a doctor's office They are, however, extremely severe cases

Of the miscellaneous group of cases which we traced to some tangible substance, I think we have relieved all, either through avoidance of cause or with treatment with the specific agent responsible for the illness

I am highly enthusiastic over the results which can be accomplished by therapy in asthma if the case can be worked out along broad lines I believe, however, success depends on a broad study of a case with treatment as indicated by the result of examination

It will be seen that opinions range from the belief that absolute permanent cure in asthma is unobtainable (Gottlieb) to an assertion of 100 per cent of pollen cases cured (Duke)

In his letter as in his writing, Duke uses the term "cure" but not in the sense of complete or absolute cure in which the patient does not require any further treatment He says a rather large proportion of persons inherit a constitution which makes it possible for them to become hypersensitive to foreign substances Once sensitive, they are likely to react in characteristic ways whenever they come in intimate contact with the substances to which they are sensitive <sup>40</sup>

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<sup>40</sup> Duke Food Allergy as a Cause of Illness, J A M A 81 886 (Sept 15) 1923

It is apparent, therefore, that the term "cure" is used with different significations by the various writers. In some replies, cure is assumed to be synonymous with temporary relief from symptoms. Since such temporary relief is often spontaneous, a great deal of the success attributed to treatment must be discounted.

The term "cure" is definite in its significance. It means to heal, to restore to sound health, to subdue or remove an ailment by remedial means. A method of treatment or a medicine cannot be held to be a cure if it does not entirely eliminate the disease from the body. We do not speak of a cure of Hodgkin's disease, or of cancer, or of diabetes mellitus unless the pathologic background of the condition is effaced and the person continues to maintain normal health without further treatment. It is in this way that we must apply the term "cure" to bronchial asthma. And, thus far, by all the methods that have been created, a cure has not been discovered.

Walker's letter represents his opinion substantially as do his excellent contributions to the literature on the subject.

Piness' letter contrasts somewhat with the following conclusions expressed by him in an earlier paper.<sup>41</sup>

The hypersensitive state may be present at birth, inherited, or conveyed by the mother to the child. A history of eczema, urticaria, or hay-fever bears a definite relationship to the protein sensitive asthmatic. Bronchial asthma is no longer an incurable condition, since by scientific study with cooperation on the part of the patient and persistency on the part of the physician, the greater percentage of sufferers can be permanently or partially relieved.

#### HEREDITY IN BRONCHIAL ASTHMA

In an article on the curability of asthma, Tracy paints a background of hereditary susceptibility to asthma, and then proceeds to advise measures to alter the constitution and metabolism of the person.<sup>42</sup> The means he advocates are radical change in the patient's intellectual groundwork, change in the patient's surroundings, change of his intestinal flora and radical change in food, both in kind and quantity, and a change of life's habits, he hopefully concludes that "bronchial asthma is curable." Recognizing that measures of constitutional treatment of bronchial asthma are visionary, and unpractical, he justifies their use by "the inadequacy of symptomatic treatment, and the consequent opprobrium to medicine."

The importance of constitutional predisposition and the conspicuousness of the family tendency in this disease has long been recognized.<sup>38</sup>

The bronchial constriction in the attack is aroused either peripherally, reflexly or directly from the central nervous system. It can hardly be

41 Piness. *Southwestern Med* 6:287 (Aug.) 1922.

42 Tracy. *New York M. J.* 105:149 (Jan. 27) 1917.

doubted that, given a certain predisposition, asthmatic attacks are brought about in all these ways <sup>43</sup>

The significance of heredity is tersely asserted by Coca when he defines allergy as "A natural inherited condition of hypersensitiveness which affects only human beings and is not dependent in any way on immunologic antibodies" <sup>8</sup>

#### STATISTICAL ANALYSES

In the analyses of cases of bronchial asthma, the family history, often recorded as negative, is based on fallacious data. On closer investigation, it will be found, as I shall now demonstrate, that most of these patients do not adequately know their family history. In a careful tabulation, it will be found, as Talbot found in his series of nineteen children, that all patients have a positive family history <sup>44</sup>. The subject therefore changes its field of interest from the anaphylactic one to the study of the germ cells and their genetic characters. The study of hereditary tendencies in human beings cannot be achieved alone by the family anamnesis of the person, since the ancestry of the family is usually known for only one entire generation. The results appear capricious because the ancestral history as given is often recorded as fact, when in reality it is not known.

In the statistical discussion on heredity in the series of 350 cases reported by Coke in England asthma is shown to be comparatively rare, occurring in a well-marked form in perhaps from 1 to 500 of the population <sup>45</sup>. Of the whole series of 350 cases, 162, or 46 per cent, gave a family history of asthma and hay-fever, seventy men and ninety-two women. Of the 182 patients who were sensitive, 103, or 56 per cent, gave positive family histories, and seventy-nine, or 44 per cent, did not, 109 patients gave neither family history nor any dermal reactions.

Analyzing his records, sixty-three patients had asthma, seventeen true seasonal hay-fever, fourteen eczema or urticaria, six migraine, sixty-five patients had brothers or sisters with asthma, hay-fever, eczema, and fifty-nine patients had one or more grandparents who had asthma or hay-fever.

The outstanding feature of supreme importance in these cases is their hereditary tendency. About 50 per cent of the cases studied by Salter, <sup>8</sup> Rackemann, <sup>33</sup> Adkinson, <sup>46</sup> and Cooke and Vander Veer <sup>47</sup> gave a hereditary history in the diseases or in associated conditions such as

<sup>43</sup> Goodhart and Spriggs. In Allbutt and Rolleston's "System of Medicine," 5 54, 1909.

<sup>44</sup> Talbot. Boston M & S J 175 191 (Aug 10) 1916.

<sup>45</sup> Coke, F. Asthma, New York, William Wood & Co., 1923.

<sup>46</sup> Adkinson. The Behavior of Bronchial Asthma as an Inherited Character, Genetics 5 363 (Jul 5) 1920.

<sup>47</sup> Cooke and Vander Veer. J Immunol 1 201 (June) 1916.

eczema, urticaria, hay-fever and others. From their studies, it became evident that the theoretic requirements of the mendelian law are approximated. The analysis of Cooke and Vander Veer suggested that sensitization is inherited as a dominant characteristic.

Sensitive cases are more likely to give positive family histories.<sup>48</sup>

In dealing with human beings the conditions are not precise enough for absolute accuracy. It is not possible to be sure that a person is pure-sensitized or mixed. If the sensitization trait is pure in one parent, all the offspring should be sensitized whether the trait in the other parent is pure or mixed.

In regard to those cases of asthma in which there is an absence of sensitization in the family history, nothing can be said. It can only be surmised that here the failure to find the antecedent sensitization was owing to the limitations of the methods of ascertaining the family histories in this respect.

Of 144 patients with bronchial asthma under my observation, I obtained a positive history in seventy cases, or 48 per cent, and a negative history in seventy-four cases, or 52 per cent. Taken at their face value, these figures are parallel to those obtained by most other workers in this field.

I hold, however, to the belief that these figures cannot be taken to mean what is usually implied for the following reason. Of the seventy-four cases with a negative history, the largest number showed a markedly incomplete knowledge of their ancestry or their lateral kin. A large proportion of these also were members of numerically small families from which, of course, data should not be used for statistical purposes. Moreover, a number of these histories must be considered unreliable when they are negative, whereas a definite positive hereditary history is not questionable.

Other interesting figures analyzed from the group of seventy positive cases are as follows. There were thirty-six men who had asthma and thirty-four women. Inheritance was from the father in twenty-one cases, of which twelve of the patients were men and nine women. Inheritance was from the mother in twenty-two cases, of which nine of the patients were men and thirteen women. It is to be seen that forty-three cases, or 61 per cent, were transmitted from the immediate parentage, suggesting the asthma in these cases to be a dominant factor in the mendelian sense. This is increased by the group of eight other patients who had children affected with asthma, making the percentage of dominant transmission seventy-three. There were nine cases of inheritance from grandparents. This number is augmented by additional

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<sup>48</sup> Longcope. Protein Hypersensitiveness and Its Importance in the Etiology of Disease, *J A M A* **77** 1535 (Nov. 12) 1921, *Am J M Sc* **152** 625 (Nov.) 1916.

ten cases in which the inheritance was through lateral kin, that is, in nineteen cases, or 27 per cent, the asthma was a recessive factor. Twenty-four patients had brothers or sisters with asthma or hay-fever.

The general principles expressed by Cooke and Vander Vee are based on careful analyses. I believe, however, that in reasoning from statistics there is always the danger of introducing fallacies. The important conclusion from their studies is that artificial sensitization is not easy to accomplish. Natural sensitization is transmitted to offspring as an unusual capacity for developing bioplastic reactivities to any foreign protein. The term "cure" is incorrect and misleading, and therefore should not be used in any discussion of results. The protection afforded by active immunization should not be expected to be permanent in any sense. These patients do not return to a normal state as a result of any form of treatment. The final solution in discovering the genesis of bronchial asthma lies in the phenomena of heredity.

#### SUMMARY

Reports of the benefit derived from the various methods of treatment of bronchial asthma are extremely diverse. Thus far, no method of treatment seems to have greatly influenced the course of the disease, which is naturally variable.

In its etiology, anaphylaxis may be dismissed from consideration. Protein sensitization is indeed a phenomenon in this disease, but it apparently is not the basic cause of the condition. It is true that the sensitization tests indicate intoxication by some substance or substances, usually protein in nature, but treatment for purposes of desensitization or immunization is futile in the endeavor to obtain an absolute cure.

The relation of nasal disease to asthma shows evidence of a constitutional susceptibility rather than a causal relationship, just as do vagotonia, hemoclastic crises and all the other theories thus far advanced as causative of asthma.

The final solution in discovering the genesis of bronchial asthma lies in the phenomena of heredity. The condition is rooted in the biologic and physicochemical structure of the chromosomes. A hereditary factor is present, not in a certain fraction of the cases, but in 100 per cent of the cases. The fallacies of statistics on heredity in human beings are well established and depend mainly on the insufficient knowledge of ancestry in cases of bronchial asthma.

#### CONCLUSIONS

An absolute cure of asthma is, therefore, not to be expected until a method has been found which will alter the chromosomal constitution either in the adult or, more radically, in the genetic cells.

# ETIOLOGIC FACTORS IN DIABETES

## PAPER II

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In a preceding article, the subject of hereditary tendency in diabetes<sup>1</sup> was discussed, with the concluding thought that diabetic patients present certain physical characteristics, and that these characteristics in reality are constitutional watermarks

In searching further for etiologic factors in diabetes, I made a survey of all preceding diseases in a group of 226 diabetic patients. This survey deals especially with infectious diseases experienced prior to the onset of diabetes, and is part of a general study concerning the relationship of acute infection to chronic diseases

To this end, a statistical study of the history of the disease was made in 1,530 unselected medical cases. From these patients my co-workers and I obtained a complete history of all the known previous diseases. Each patient was given a questionnaire to be filled in at home, with the assistance of the family, which we believe increases the accuracy of such records

The type and proportion of the various diseases diagnosed in these 1,530 patients are shown in the table

### INCIDENCE OF VARIOUS DISEASES IN PATIENTS STUDIED

Diabetes	226
Gastro-intestinal diseases	192
Neuroses	177
Cardiovascular (organic) diseases	171
Endocrine disturbances	156
Arterial hypertension	143
Pulmonary infections	135
Focal infections	110
Diseases of nutrition	96
Acute and subacute nephritis	67
Syphilis	57
	<hr/>
	1,530

Chart 1, which gives the frequency curve of all diseases, was constructed from the tabulated results of these records

As will be seen, measles was the most common of the acute infections, this was followed by pertussis and varicella. Next in frequency was tonsillitis, although higher figures for tonsillitis would not have been

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1 Barach, Joseph H. Constitutional and Hereditary Traits in Diabetics, *Am J M Sc* **172** 243 (Aug) 1926

surprising. It is assumed that the figures in the table indicate those cases in which attacks were recurrent and troublesome. The figures for influenza probably include some cases of the grip, the terms being used interchangeably by both physician and patient. Those for typhoid fever may seem high, this is due to the fact that for many years typhoid fever was pandemic in Pennsylvania and adjacent states. The charts include tonsillectomy for the purpose of indicating tonsillar disease sufficiently troublesome to warrant operation. Surgical operations and serious

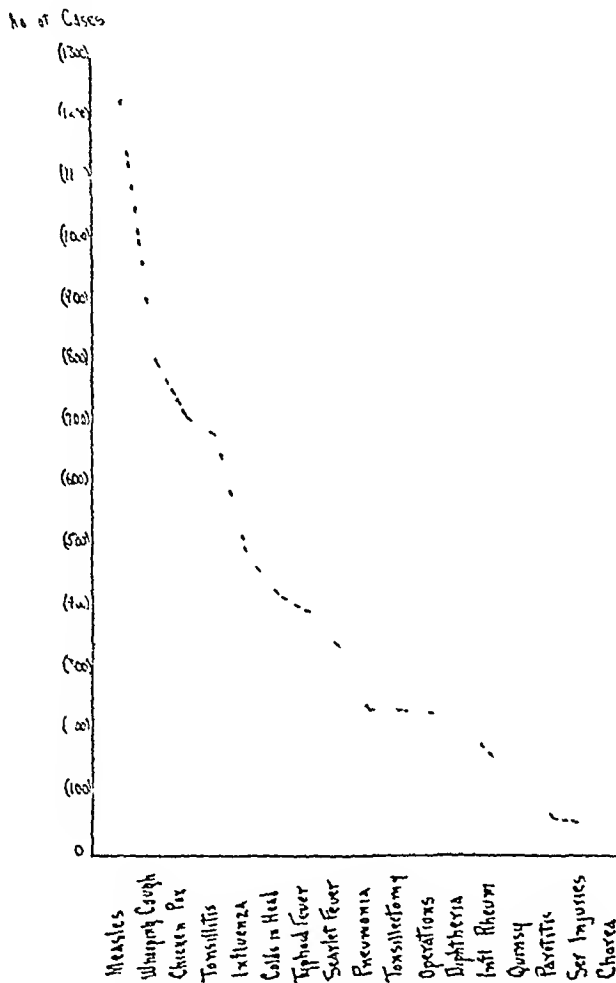


Chart 1—Curve for all diseases—1,530 cases

injuries are also recorded. As the chart shows, the curve is arranged on the basis of frequency, the most common infection first, and the least frequent ones last.

*Neuroses*—For the purpose of comparison with chart 1 for all diseases, a curve is shown made up of a mixed group of 177 cases classified as neuroses (chart 2). These patients were free from other discoverable disease. They were cases of psychasthenia, neurasthenia, psychoneuroses and neurocirculatory asthenia. Diagnoses were made after organic diseases had been eliminated as far as possible and when it was impossible

to make more definite diagnoses. It is interesting to note how well this curve of the nondescript group corresponds to the all disease curve, exceeding it only in the greater number of tonsillectomies. This is explainable when one recalls how such patients go from one physician to another seeking relief, and are sooner or later advised to submit to tonsillectomy.

*Pulmonary Infections*—Contrasted to the all disease group and the neuroses group a curve based on a series of 135 cases of pulmonary

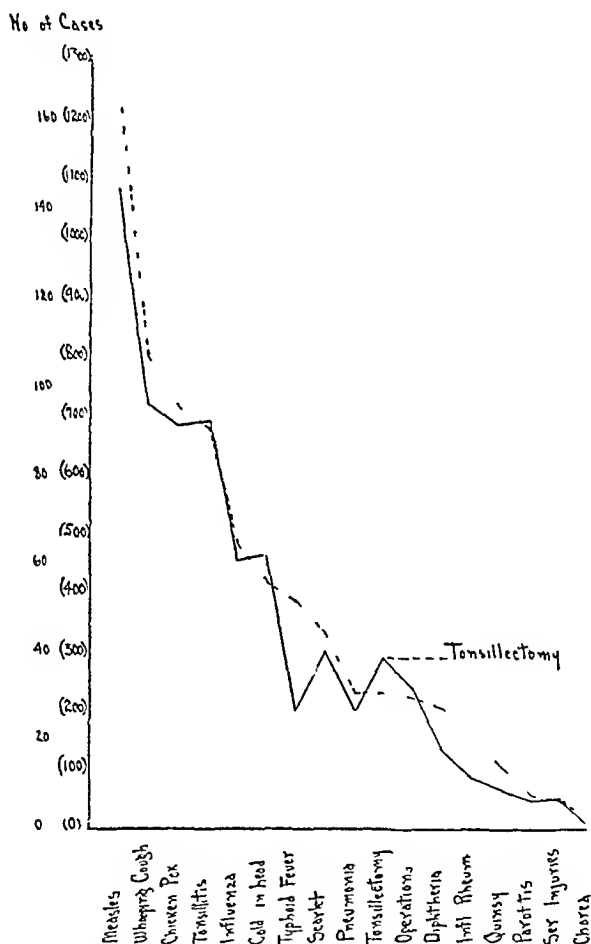


Chart 2—A comparison of the all disease curve and the neuroses curve—177 cases. The broken line indicates the all disease curve, the unbroken line, the neuroses curve.

infections is presented (chart 3). This group includes tuberculous and nontuberculous pulmonary infections. It may be seen at a glance that the diseases in this group which exceed those of the all disease curve, correspond to the physician's daily experiences in this type of case. Tonsillitis, colds in the head and pneumonia are the characteristic complaints of patients with pulmonary disease.

*Gastro-Intestinal Cases*—This group includes 192 gastro-intestinal cases. The curve of these gastro-intestinal cases exceeds the all disease

curve strikingly in the number of operations (chart 4) These operations were generally performed for diseases of the appendix, gallbladder, stomach or duodenum The curve conforms well to what may be expected in this type of patient

*Diabetes*—In a group of 362 cases of diabetes, the diabetic curve shows an excess over the all disease curve in chronic tonsillitis and in typhoid fever (chart 5) I believe this to be of clinical significance It is a striking experience to find enlarged and diseased tonsils in every

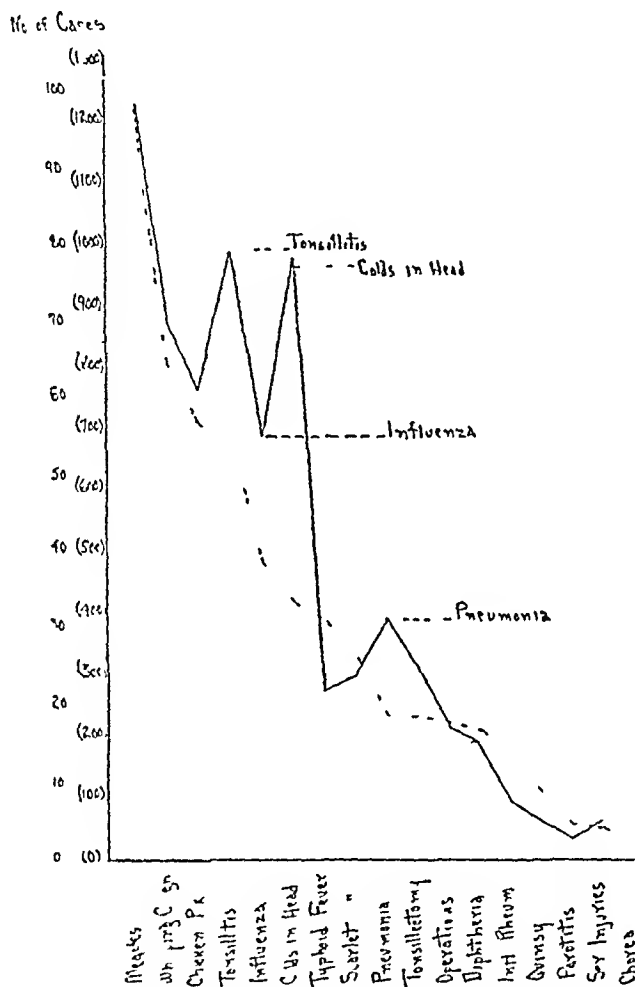


Chart 3—A comparison of the all disease curve and the pulmonary infection curve, including 135 cases of tuberculosis, asthma and bronchitis The broken line indicates the all disease curve, the unbroken line, the pulmonary infection curve

third person with diabetes that one examines, the total number of cases being 114 In the last 226 cases of diabetes in which the previous history of the disease was complete, there was a history of recurrent tonsillitis and the presence of diseased tonsils at the time of physical examination in 107 cases, almost one half the total number All this seems especially significant when one recalls that these persons have carried diseased tonsils into the fourth and fifth decade of life A focal infection of

thirty or forty years' duration, even if intermittent, is injurious. This assumption is understood in the light of what is known of the insulin disturbance which occurs in patients with diabetes during acute infections of any kind.

Typhoid fever, as the curve clearly shows, had occurred in these diabetic patients with unusual frequency. That a relationship may exist between typhoid fever and diabetes is further suggested by the fact that a hyperglycemia is present in the course of the disease and by evidences

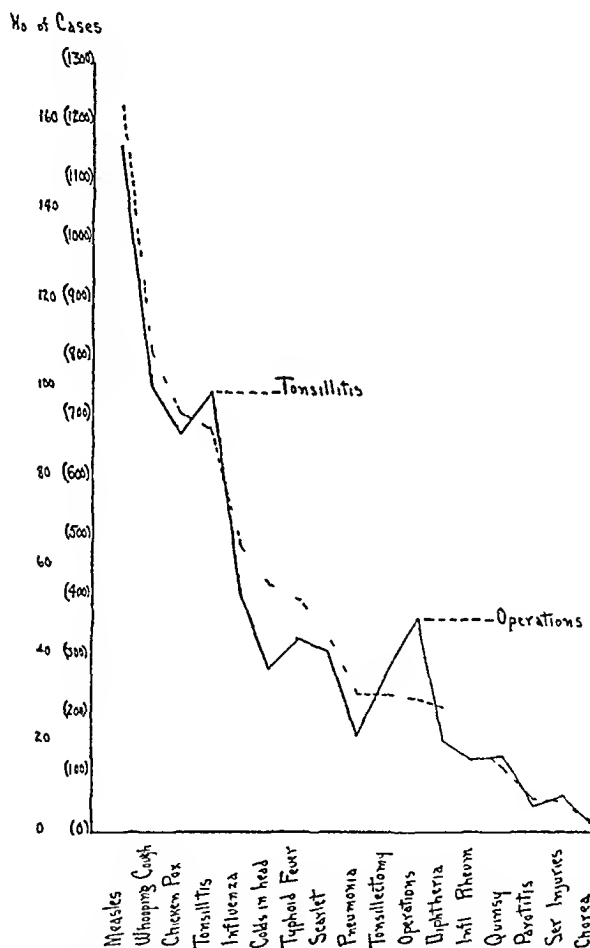


Chart 4—A comparison of the all disease curve and the gastro-intestinal curve—192 cases. The broken line indicates the all disease curve, the unbroken line, the gastro-intestinal curve.

of a definite metabolic change which follows convalescence from the disease. Posttyphoid obesity is just as striking as prediabetic obesity. It is possible that both are due to a similar underlying cause, some pathologic change in the insulin producing tissues.

#### SUMMARY AND DISCUSSION

In order to study the infections as possible etiologic factors in diabetes, a curve was constructed indicating the relative frequency of all

preceding infectious diseases in 1,530 patients. My co-workers and I compared disease frequency in a nondescript group of neurotic patients with the all disease curve and found no divergence in the curves. A group of cases of pulmonary infection shows that such patients suffer most frequently from tonsillitis, acute colds and pneumonia. A group of patients with gastro-intestinal diseases shows excess in operative cases, such as appendectomy, gallbladder, gastric and duodenal operations. These and other charts not included here show the validity of the all

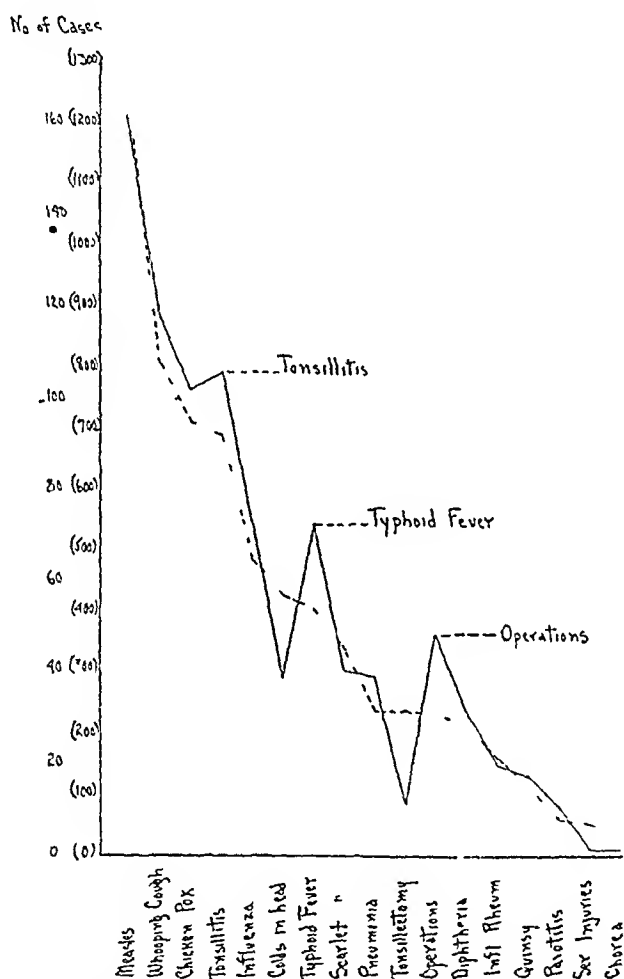


Chart 5—A comparison of the all disease curve and the diabetic curve—226 cases. The broken line indicates the all disease curve, the unbroken line, the diabetic curve.

disease curve, and indicate that any marked deviation from this curve has definite clinical significance. The special group considered here, that of diabetic patients, shows a marked increase in the number of cases of chronic tonsillar disease and typhoid fever.

Attempting to interpret these two deviations from the all disease curve, my co-workers and I were led to believe that in chronic tonsillar disease repeated strain on the insulin-producing tissues, as must occur with each fresh attack, undoubtedly has its injurious effect. The con-

tinued effect of a chronic infection is less apparent. Typhoid fever is an acute infectious disease of such duration and severity as could be the cause of permanent injury to the pancreas and other tissues.

Physicians who treat diabetic patients in considerable numbers know that an intercurrent acute infection reduces carbohydrate tolerance to one half or even more than one half of the normal tolerance for that person. Whether strain on the insulin-forming tissues results from frequently recurring infections, or whether it results from a severe and prolonged acute infection such as typhoid fever, the strain imposed on an organism endowed with hereditary tendency to diabetes may be sufficient to transform the potential into a case of real diabetes.

# RELATION BETWEEN CELL COUNT, CELL VOLUME AND HEMOGLOBIN CONTENT OF VENOUS BLOOD OF NORMAL YOUNG WOMEN

REDETERMINATIONS OF COLOR INDEX, VOLUME INDEX AND  
SATURATION INDEX STANDARDS BASED ON OBSERVA-  
TIONS IN ONE HUNDRED CASES <sup>1</sup>

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The need for a definite accepted figure, expressed in grams per one hundred cubic centimeters, as the standard of average hemoglobin content of normal blood has been emphasized recently <sup>1</sup>. Few physicians, however, realize that the figures usually given in the texts for average normal red cell counts (5 million for men and 4.5 million for women) are apparently based on only four blood examinations made in 1852 <sup>2</sup> and 1854 <sup>3</sup> by methods which are now obsolete. These figures have since been copied from one textbook to another without experimental confirmation. The increasing use of volume index, saturation index and color index determinations in the differential diagnosis of anemia demands that the normal averages and ranges of variation in these observations be determined accurately.

In this article we present the results of accurate red cell counts, hemoglobin determinations and cell volume determinations on 100 healthy young women, and give the average and range of variation of the corresponding indexes.

As the methods used are identical in every detail with those used in a previous research on the normal standards in healthy young men, the details of the technic are omitted here, and the reader is referred to our previous article <sup>4</sup>.

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<sup>1</sup> From the Department of Biochemistry, University of Oregon Medical School.

<sup>1</sup> Editorial: The Need for a Fixed Hemoglobin Standard, *J Lab & Clin Med* **11** 696 (April) 1926. Lindsay, J W, Rice, E C, and Selinger, M A. A Plea for a Standardized Method of Estimating and Reporting Hemoglobin Values, *ibid* **11** 737 (May) 1926.

<sup>2</sup> Vierordt, K. *Zählung der Blutkörperchen des Menschen*. Arch f physiol Heilk, Stuttgart **11** 327, 1852.

<sup>3</sup> Welcker, H. *Ueber Blutkörperchenzahlung*, Arch d Ver f gemeinsch Arb u Ford d wissensch Heilk, Göttingen **1** 161, 1854.

<sup>4</sup> Osgood, E E. Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *Arch Int Med* **37** 685 (May) 1926.

## SUBJECTS EXAMINED

One hundred young women between the ages of 18 and 30 were studied. With the exception of a few medical students, all were nurses, which explains the slightly lower average age than that of the men studied.

Figure 1 shows at a glance the age distribution of the women and of the men studied previously. As there were no men 18 years of age in our series, we have noted the average of the results on the twelve women of this age separately for comparison (bottom of table 1). Note that they do not differ significantly from the averages for the total 100 cases.

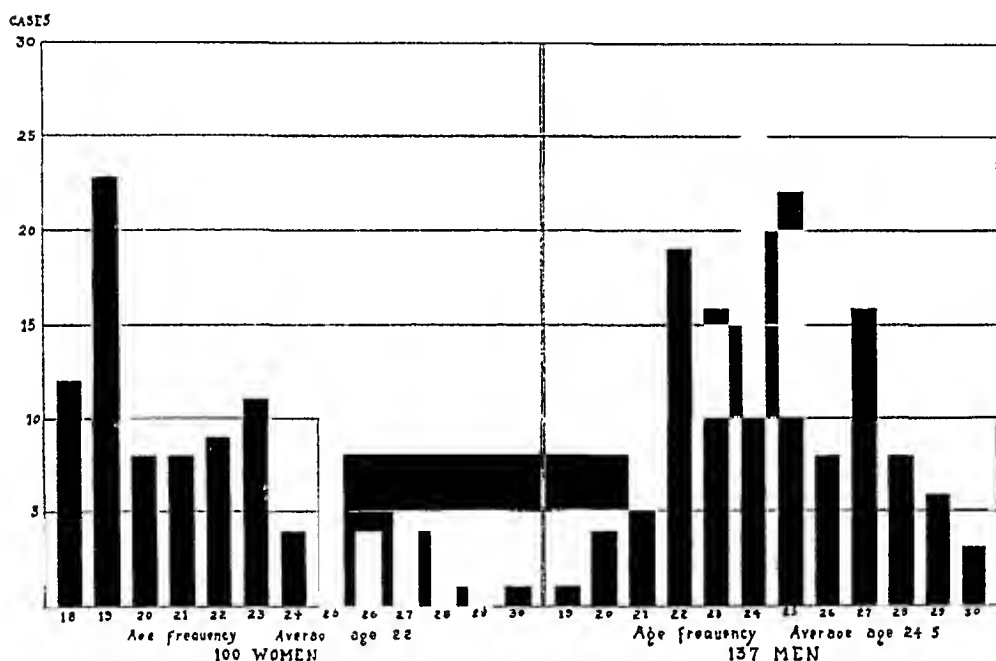


Fig 1—Age distribution

For comparison we have also inserted the averages previously reported on 137 men between 19 and 30 years of age.<sup>4</sup>

Each of the subjects felt well at the time the blood was drawn, and as practically all of them had had a complete medical examination within a year, it is safe to say that they were in good health when examined. To avoid any possible temporary influence of menstruation on the results, examinations were not made during the menstrual period or during the week following it. The height, weight and nationality of each subject were recorded, but are not included in the table, as these data are not used in this article. The great majority were American born of American parents. Most of the others were American born of foreign born parents, including chiefly Irish, Scotch, English, Scandinavian and German. There were not enough of any one nationality to justify an analysis on this basis.

Most of the specimens of blood were drawn between 8 and 9 o'clock in the morning in the fall of the year. However, a particular effort was not made to take the specimens of blood at the same time of the day or year, as this is not done in clinical practice, and as we wished to determine the full range of normal variation. All the subjects examined reside at an altitude of less than 500 feet.

#### THE RED CELL COUNT IN NORMAL WOMEN

A survey of the literature to date (October, 1926) shows that reasonably accurate red cell counts have been reported for only eighteen normal women whose ages were specifically mentioned as being between 18 and 30. They are distributed as follows:

Bierring<sup>5</sup> 3 women, averaging 4.24 million  
 Gram and Norgaard<sup>6</sup> 6 women, averaging 4.59 million  
 Haden<sup>7</sup> 9 women, averaging 4.33 million  
 Total 18 women, averaging 4.33 million

The number of women studied is too small to impart any great significance to the average. In addition, the following presumably accurate counts on 194 women were found in the literature, but without any statement concerning ages:

Bie and Møller<sup>8</sup> 10 women, averaging 4.74 million  
 Bing<sup>9</sup> 51 women, averaging 4.9 million  
 Gram<sup>10</sup> 56 women, averaging 4.78 million<sup>11</sup>  
 Larrabee<sup>12</sup> 9 women, averaging 4.97 million  
 Six other authors<sup>13</sup> 68 women, averaging 4.81 million  
 Total 194 women, averaging 4.83 million

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5 Bierring, K. Svingninger i Erythrocyttallet hos normale Mennesker, *Ugeskr. f. Læger* **82** 1445 (Nov. 18) 1920.

6 Gram, H. C., and Norgaard, A. Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, *Arch. Int. Med.* **31** 164 (Feb.) 1923.

7 Haden, R. L. The Normal Hemoglobin Standard, *J. A. M. A.* **79** 1496 (Oct. 28) 1922, Accurate Criteria for Differentiating Anemias, *Arch. Int. Med.* **31** 766 (May) 1923.

8 Bie, V., and Møller, P. Undersøgelser af normale Menneskers Blod, *Ugeskr. f. Læger* **75** 749, 817 and 878, 1913, Le sang humain normal, *Arch. d. mal. du cœur* **15** 177 (April) 1922.

9 Bing, H. I. On the Number of Red Blood Corpuscles at Different Ages and Under Different Circumstances, *Proc. Ninth Northern Congress Int. Med., Acta med. Scandinav.* **53** 833 (Jan.) 1921.

10 Gram, H. C. Om det normale Erythrocyttale og den normale Hemoglobinmængde i Venesblod, *Ugeskr. f. Læger* **82** 1543 (Dec. 9) 1920, On the Standardization of Hemoglobinometers and Its Importance for Index Calculation, *Acta med. Scandinav.* **57** 27 (Nov.) 1922.

11 Gram states that his subjects were nurses, so it is probable that his age distribution was similar to ours. Note the close agreement of our average figure (4.8) with his (4.78).

12 Larrabee, R. C. The Volume Index of the Red Corpuscles, *J. M. Research* **24** 15 (Jan.) 1911.

13 Quoted by Bie and Møller (footnote 8).

The close agreement of this average with our average (4.8) suggests either that these workers chose subjects in the same age group as ours, or that there is little variation with age of the average red cell count in normal adult women. These reported counts range from 4 million to 5.9 million. Our lowest count was 4.07 million, and the highest was 5.55 million.

TABLE 1—*Blood Observations in One Hundred Normal Young Women*

Subject	Age	Red Cell Count, Millions per C mm	Hemoglobin, Grams per 100 Cc	Hemoglobin per 100 Cc per 5 Million Cells	Color Index	Volume of Cells per 100 Cc	Volume of Cells per 100 Cc per 5 Million	Volume Index	Saturation Index
1	22	4.63	10.98	11.86	0.83	35.29	38.11	0.89	0.93
2	22	5.00	12.27	12.27	0.86	36.96	26.96	0.86	1.00
3	21	4.73	12.09	12.78	0.89	38.54	40.74	0.95	0.94
4	22	4.91	12.67	12.90	0.90	42.63	43.42	1.01	0.89
5	25	4.65	12.08	12.98	0.91	37.02	39.80	0.93	0.98
6	23	4.53	11.81	13.04	0.91	35.18	38.83	0.91	1.00
7	18	5.00	13.04	13.04	0.91	38.28	38.28	0.89	1.02
8	20	4.38	11.45	13.08	0.91	36.52	41.69	0.97	0.94
9	23	5.22	13.66	13.09	0.92	42.21	40.43	0.94	0.98
10	19	5.13	13.50	13.15	0.92	41.18	40.13	0.94	0.98
11	18	5.15	13.70	13.30	0.93	40.05	38.88	0.91	1.02
12	19	4.75	12.74	13.41	0.94	41.90	44.10	1.03	0.91
13	25	5.38	14.43	13.42	0.94	44.16	41.04	0.96	0.98
14	27	5.18	13.91	13.43	0.94	41.32	39.88	0.93	1.01
15	26	4.39	11.81	13.45	0.94	37.27	42.46	0.99	0.95
16	19	5.00	13.48	13.48	0.94	41.37	41.37	0.97	0.97
17	26	5.26	14.19	13.48	0.94	44.36	42.17	0.99	0.95
18	19	5.21	14.17	13.52	0.95	43.90	41.89	0.98	0.97
19	19	5.51	14.93	13.55	0.95	44.05	39.97	0.93	1.02
20	24	4.91	13.40	13.56	0.95	44.87	45.42	1.06	0.90
21	25	4.22	11.47	13.59	0.95	39.47	46.77	1.09	0.87
22	23	4.64	12.65	13.64	0.95	41.65	44.88	1.05	0.90
23	23	5.08	13.86	13.64	0.95	40.51	39.87	0.93	1.02
24	19	5.22	14.27	13.67	0.96	40.00	38.31	0.90	1.07
25	22	5.51	15.07	13.67	0.96	45.22	41.03	0.96	1.00
26	19	5.00	13.68	13.68	0.96	42.08	42.08	0.98	0.98
27	18	4.85	13.29	13.70	0.96	42.43	43.74	1.02	0.94
28	25	4.07	11.15	13.70	0.96	37.50	16.07	1.08	0.89
29	19	4.82	13.26	13.76	0.96	42.08	43.65	1.02	0.94
30	25	5.22	14.38	13.77	0.96	42.25	40.47	0.95	1.01
31	22	5.55	15.30	13.79	0.96	43.70	39.37	0.92	1.04
32	19	5.05	13.98	13.84	0.97	42.50	42.08	0.98	0.99
33	22	4.75	13.18	13.87	0.97	40.26	42.38	0.99	0.98
34	23	4.56	12.70	13.92	0.97	37.18	40.77	0.95	1.02
35	21	5.30	14.77	13.93	0.97	43.54	41.08	0.96	1.01
36	27	5.21	14.53	13.95	0.98	41.08	39.42	0.92	1.07
37	26	4.96	13.86	13.97	0.98	42.00	42.34	0.99	0.99
38	19	4.78	13.36	13.97	0.98	40.10	41.95	0.98	1.00
39	20	4.74	13.26	13.99	0.98	41.45	43.73	1.02	0.96
40	25	4.67	13.08	14.01	0.98	39.84	42.66	1.00	0.98
41	30	4.81	13.48	14.02	0.98	42.04	42.70	1.00	0.98
42	18	4.80	13.47	14.03	0.98	42.25	44.01	1.03	0.95
43	21	1.43	12.53	14.14	0.99	39.25	44.30	1.04	0.95
44	21	5.22	14.77	14.14	0.99	42.57	40.78	0.95	1.04
45	20	4.74	13.43	14.16	0.99	42.07	44.37	1.04	0.95
46	27	4.80	13.59	14.16	0.99	39.84	41.50	0.97	1.02
47	20	4.91	13.97	14.22	0.99	41.73	42.50	0.99	1.00
48	21	4.93	14.05	14.25	1.00	40.91	41.49	0.97	1.03
49	28	4.64	13.25	14.28	1.00	40.77	43.93	1.03	0.97
50	21	4.89	13.99	14.31	1.00	42.82	43.78	1.02	0.98
51	19	4.88	13.97	14.31	1.00	40.61	41.61	0.97	1.03
52	23	4.14	11.87	14.35	1.00	37.92	45.80	1.07	0.93
53	19	4.80	13.80	14.37	1.00	40.81	42.51	0.99	1.01
54	28	4.45	12.79	14.37	1.00	39.49	44.37	1.04	0.96
55	19	4.46	12.85	14.40	1.01	39.16	43.90	1.03	0.98
56	25	4.94	14.30	14.47	1.01	41.80	42.30	0.99	1.02
57	28	5.10	14.77	14.48	1.01	43.43	42.68	1.00	1.01
58	19	4.81	13.94	14.49	1.01	40.86	42.48	0.99	1.02
59	25	4.69	13.59	14.49	1.01	39.59	42.20	0.99	1.02
60	27	4.59	13.32	14.51	1.02	36.42	39.68	0.93	1.10
61	24	4.33	12.57	14.52	1.02	41.04	47.39	1.11	0.92
62	19	4.73	13.76	14.54	1.02	40.76	43.09	1.01	1.01
63	29	4.60	13.39	14.55	1.02	37.71	40.99	0.96	1.06
64	19	4.35	12.65	14.55	1.02	38.50	44.25	1.03	0.99
65	21	4.74	13.80	14.56	1.02	41.78	44.07	1.03	0.99

TABLE 1—*Blood Observations in One Hundred Normal Young Women—Continued*

Sub ject	Age	Red Cell Count, Millions per C mm	Hemo- globin, Grams per 100 Cc	Hemoglo- bin per 100 Cc per 5 Million Cells	Color Index	Volume of Cells per 100 Cc	Volume of Cells per 100 Cc per 5 Million	Volume Index	Satu- ration Index
66	25	4.79	13.98	14.59	1.02	44.71	46.67	1.09	0.94
67	19	4.95	14.46	14.61	1.02	45.89	46.35	1.08	0.94
68	27	5.34	15.64	14.64	1.02	46.23	43.38	1.01	1.01
69	20	4.64	13.59	14.65	1.02	39.29	42.33	0.98	1.03
70	18	4.49	13.18	14.68	1.03	40.65	45.27	1.06	0.97
71	24	5.37	15.77	14.69	1.03	43.14	40.17	0.94	1.10
72	24	5.02	14.79	14.73	1.03	45.00	44.82	1.05	0.98
73	23	4.86	14.35	14.77	1.03	42.49	43.71	1.02	1.01
74	23	4.53	13.40	14.79	1.03	40.37	44.56	1.04	0.99
75	23	4.49	13.31	14.81	1.04	40.56	45.17	1.05	0.99
76	20	4.68	13.87	14.82	1.04	41.33	44.15	1.03	1.01
77	28	4.54	13.48	14.85	1.04	39.64	43.88	1.03	1.01
78	26	4.39	13.05	14.87	1.04	41.22	46.95	1.10	0.95
79	19	4.38	13.08	14.93	1.04	35.32	40.32	0.94	1.11
80	18	5.04	15.06	14.94	1.04	44.56	44.21	1.03	1.01
81	19	4.70	14.05	14.95	1.05	43.59	46.37	1.08	0.97
82	18	4.91	14.53	15.03	1.05	43.54	44.07	1.03	1.02
83	18	4.54	13.69	15.08	1.05	39.33	43.32	1.01	1.04
84	18	4.48	13.52	15.09	1.06	41.84	46.70	1.09	0.97
85	18	5.13	15.57	15.17	1.06	42.21	41.14	0.96	1.10
86	22	5.04	15.30	15.19	1.06	43.39	43.14	1.01	1.05
87	20	4.30	13.12	15.26	1.07	38.44	44.70	1.04	1.03
88	22	4.46	13.76	15.42	1.08	40.71	45.64	1.07	1.01
89	19	4.95	15.29	15.44	1.08	44.10	44.55	1.04	1.04
90	25	4.51	13.94	15.45	1.08	38.69	42.90	1.00	1.08
91	18	4.77	14.78	15.49	1.08	39.45	41.35	0.97	1.11
92	21	4.58	14.20	15.50	1.08	41.41	45.21	1.06	1.02
93	18	4.88	15.14	15.51	1.09	39.34	40.31	0.94	1.16
94	23	4.62	14.43	15.62	1.09	42.54	46.04	1.08	1.01
95	19	4.63	14.77	15.95	1.12	41.54	44.86	1.05	1.07
96	20	4.19	13.89	15.97	1.12	39.80	47.50	1.11	1.01
97	23	4.37	13.99	16.01	1.12	40.36	46.17	1.08	1.04
98	19	5.13	16.49	16.07	1.12	45.33	44.18	1.03	1.09
99	22	4.49	14.46	16.10	1.13	41.34	46.03	1.08	1.05
100	19	4.37	14.17	16.22	1.13	40.00	45.77	1.07	1.06
Aver	22	4.80	13.69	14.29	1.00	41.04	42.87	1.00	1.00
Average of those 18 years of age (12 subjects)	18	4.84	14.11	14.59	1.02	41.16	42.69	1.00	1.02
Average of those 19 to 30 years of age (88 subjects)	22.4	4.79	13.64	14.25	1.00	41.02	42.90	1.00	1.00
Average for men 19 to 30 years of age <sup>4</sup>	24.5	5.39	15.76	14.66	1.00	44.84	40.80	1.00	1.00

It is equally important, however, to know the actual frequency distribution of the counts. The frequency distribution of our counts is shown in figure 2. Note that about 90 per cent of the counts fall between 4.3 and 5.3 million. The average is indicated in the chart (as also in charts 3 to 7) by a column having oblique lines in its lower portion. It will be noticed that the average count is also the most frequently occurring count. The detailed results are given in the table.

Our average red cell count of 4.8 million is distinctly higher than that given for women in most texts. It is lower by 0.6 million than the average count (5.4 million) reported for males in our previous article <sup>4</sup>

## HEMOGLOBIN CONTENT OF THE BLOOD IN NORMAL WOMEN

Only a few estimations for hemoglobin which are reported in the literature are sufficiently accurate to be of value. We could find reliable estimations on only sixty-four women between the ages of 18 and 30 years, they are as follows

Williamson<sup>14</sup> (spectrophotometer) 49 women, averaging 15.11 Gm per one hundred cubic centimeters

Gram and Norgaard<sup>15</sup> (Autenrieth-Königsburger colorimeter method) 6 women, averaging 12.82 Gm

Haden<sup>7</sup> (Van Slyke's method) 9 women, averaging 13.5 Gm

Total 64 women, averaging 14.67 Gm per one hundred cubic centimeters

The wide variations between the averages reported by different authors are undoubtedly due to the small number of cases examined by each

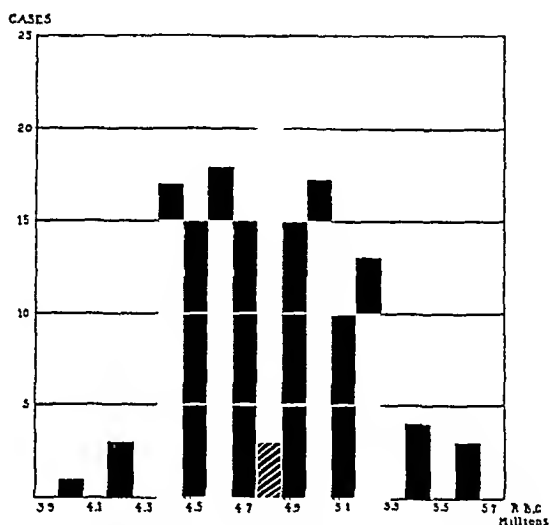


Fig 2—Red cell counts in one hundred healthy young women

In addition, we have found reports of 143 examinations of women in which the age was not stated, or in which the methods used were of doubtful accuracy. They are distributed as follows

Lundsgaard<sup>16</sup> (Palmer's method) 1 woman, averaging 13.04 Gm

Bie and Møller<sup>8</sup> (Meissling colorimeter) 10 women, averaging 13.3 Gm

Bing<sup>9</sup> (Sahl's method) 51 women, averaging 13.87 Gm

Leichtenstern<sup>16</sup> (spectrophotometer) 13 women, averaging 13.49 Gm

14 Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch Int Med* 18:505 (Oct) 1916

15 Lundsgaard, C. Studies of Oxygen in the Venous Blood, *J Biol Chem* 33:133 (Jan) 1918

16 Leichtenstern, O. Untersuchungen über den Haemoglobingehalt des Blutes in gesunden und kranken Zuständen, Leipzig, 1878. All of these subjects were between 18 and 30 years of age

Gram<sup>10</sup> (Autenrieth Hellige colorimeter) 56 women, averaging 11.87 Gm  
 Haldane<sup>17</sup> (Haldane oxygen capacity method) 12 women, averaging 12.31 Gm  
 Total 143 women, averaging 12.88 Gm

The results have all been calculated as grams of hemoglobin per one hundred cubic centimeters of blood because so many different figures are used as 100 per cent hemoglobin by manufacturers of hemoglobino-meters (thus making the percentage figure almost meaningless). Many results reported in the literature had to be discarded because the authors failed to state the method used. As Haskins and Osgood<sup>18</sup> have recently shown, many of the hemoglobin methods in common use are extremely inaccurate,<sup>19</sup> therefore, until accurate methods are universally used, every one reporting hemoglobin figures should state the method of estimation. Much confusion will be avoided if these results are always reported as grams per one hundred cubic centimeters.

By the Osgood-Haskins<sup>20</sup> method (the maximum error not being over 2 per cent) our average on 100 women between 18 and 30 years of age was 13.69 grams per one hundred cubic centimeters of blood. It will be seen from figure 3 that the average is also the most frequently occurring result, and that about 90 per cent of the results fall between 12 and 15.5 Gm. Our lowest estimation was 10.98 Gm, and the highest 16.49 Gm.

#### COLOR INDEX

The essentials for a color index determination that will be of value in diagnosis are (1) an accurate red cell count on the patient's blood, (2) an accurate hemoglobin estimation on the same blood and (3) a normal standard for comparison. This standard is the average hemoglobin coefficient in healthy persons of the same sex and in the same age group. We have previously<sup>4</sup> defined the term *hemoglobin coefficient* as

17 Haldane, J. The Colorimetric Determination of Hemoglobin, *J. Physiol.* **26** 497 (June) 1901. Five of these subjects were between 18 and 30 years of age.

18 Haskins, H. D., and Osgood, E. E. Methods of Estimating Hemoglobin, *Northwest Med.* **25** 500 (Sept.) 1926.

19 It is worthy of note that at least three of the young women included in this series had been told by reputable physicians that they had chlorosis because the hemoglobin estimation by the Dare method was around 65 per cent. In each case estimation by an accurate method showed over 12.4 Gm hemoglobin per one hundred cubic centimeters (90 per cent), and the color index was well within the normal range. On the other hand, three cases of definite chlorosis (not included in this series) with color indexes of 0.82, 0.68 and 0.67 respectively, were found which had been overlooked by other methods although the pallor was so marked in each case that we suspected the diagnosis at the time the blood was taken.

20 Osgood, E. E., and Haskins, H. D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* **57** 107 (Aug.) 1923.

“the number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter,” and we use it with this meaning. The color index is calculated by dividing the percentage of hemoglobin by the percentage of red cells. For this calculation the normal hemoglobin coefficient (for the patient’s age and sex) is considered as 100 per cent, and a red cell count of 5 million is considered as 100 per cent.

We were able to find in the literature satisfactory data for calculating hemoglobin coefficients reported for only fifteen women between 18 and 30 years of age. The results follow:

- Gram and Norgaard<sup>4</sup> 6 women, averaging 14 Gm
- Haden<sup>5</sup> 9 women, averaging 15.7 Gm
- Total 15 women, averaging 15 Gm

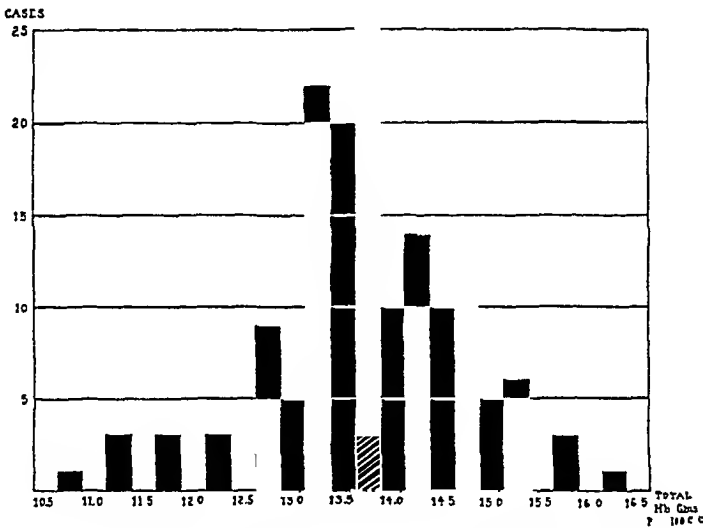


Fig. 3—Total hemoglobin in one hundred women

This number of cases is obviously too small to be of much value in determining the actual average. Our average on 100 women was 14.29 Gm. As the second decimal is not significant, we recommend 14.3 Gm as the normal hemoglobin coefficient in women and have used it as 100 per cent hemoglobin in calculating color indexes. The range of distribution is shown in frequency figure 4. The tendency to a double peak is too slight to be statistically significant. If a larger number of cases were examined, the average would undoubtedly be the most frequently occurring figure. About 90 per cent of the results fall between 13 and 16 Gm, corresponding to color indexes between 0.9 and 1.10. The lowest color index was 0.83 and the highest was 1.13.

TOTAL CELL VOLUME

Estimations of cell volume in women measured by our technic<sup>4</sup> have not as yet, been reported. Gram and Norgaard,<sup>6</sup> using a slightly dif-

ferent but equally accurate method, have reported estimations on six women (18 to 30 years old) averaging 40.4 cc, and by a less satisfactory method Haden<sup>7</sup> has reported estimations on nine women (18 to 30) averaging 39.7 cc of packed cells per one hundred cubic centimeters of blood. In addition Gram<sup>21</sup> reports an average of 41 cc, with extremes of 37 and 45 cc on twenty-five normal women (ages and red cell counts not stated). These results agree well with our average of 41 cc on 100 women. Figure 5 shows that this average is also the most frequently occurring figure and that over 90 per cent of the results fall between 37 and 45 cc. The extremes were 35.29 cc and 46.33 cc.

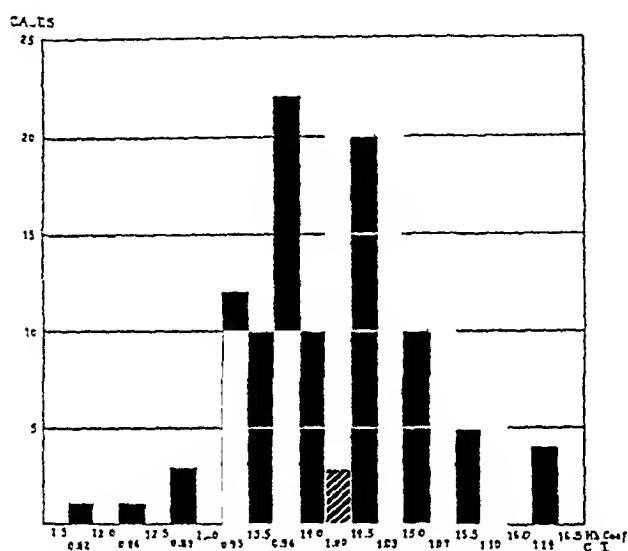


Fig. 4—Hemoglobin coefficients and color indexes in one hundred women

#### THE VOLUME INDEX

Since a high volume index is the most valuable and the most constant single laboratory finding in pernicious anemia the importance of its accurate determination cannot be overemphasized. This index expresses the ratio between the average size of the red cells in the blood examined and the average size of the red cells in the blood of healthy persons of the same sex and in the same age group. It is determined by dividing the volume of cells, expressed in per cent (the average normal volume coefficient for the patient's age and sex being taken as 100 per cent), by the percentage of red cells (5 million being 100 per cent). We have previously<sup>4</sup> defined the term *volume coefficient* as "the volume of packed red cells per hundred cubic centimeters of blood calculated to a red cell count of 5 million."

Gram and Norgaard<sup>6</sup> report the only satisfactory volume coefficients we were able to find in the literature, but they examined only six women

<sup>21</sup> Gram, H. C. A New Method for the Determination of the Fibrin Percentage in Blood and Plasma, *J. Biol. Chem.* **49**: 279 (Dec.) 1921.

in this age group Their average of 44 becomes 42.5 when 3.5 per cent is deducted<sup>22</sup> for the difference in technic, and this agrees well with our average of 42.8 We also mention Haden's<sup>7</sup> results on nine women (18 to 30 years of age), although we believe his average (46.2) is too high He neglected to centrifugalize to constant volume, and our experience has shown that his thirty minute period of centrifugalizing at 2,500 revolutions a minute is not sufficient to pack completely the cells of many normal specimens of blood Sedimentation times of normal specimens of blood vary markedly, and some are high Therefore, if actual cell volume is to be determined, we cannot overemphasize the importance of centrifugalizing until the cell volume remains constant

We must repeat our warning that the average of a small number of cases should never be taken as a standard For instance, the first twenty-five cases of our series gave a volume coefficient (43.68) higher

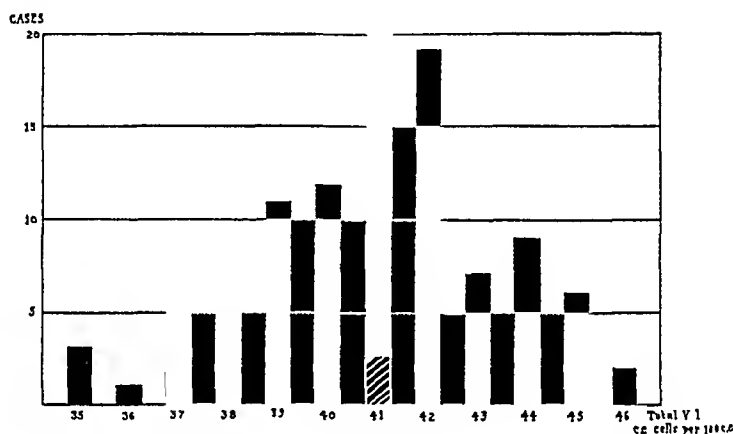


Fig 5—Total volume of cells in one hundred women

than the average for the 100 cases by 2 per cent Blood standards should not be based on a series of less than 100 cases

Our average volume coefficient on 100 women was 42.8 cc., which is significantly higher than the average figure (40.8 cc.) found previously on young men<sup>4</sup> This result was unexpected, and we have been unable to find any reason why young women should have larger cells than young men The difference is about seven times the probable error of determination, so it is unlikely that it is due to random sampling as might be the case if only a small number of cases were examined The technic used in the two series was identical in every detail, including the use of the same centrifuge and centrifuge tube Several of the estimations on women were interspersed between the estimations on men, hence a variation in technic is improbable This apparent difference should be confirmed by other workers on a large series of subjects

<sup>22</sup> The justification for this deduction has already been discussed in a previous article (footnote 4)

Reference to figure 6 shows that the extremes are 36.96 and 47.5, and that the average as well as the range of the most frequently occurring results (38.8 to 46.8) is higher than the corresponding figures for men. As the difference of five cases between the peak and the average is less than twice the probable error of the frequency, the peak of the curve would probably occur at the average in a larger series of cases. Over

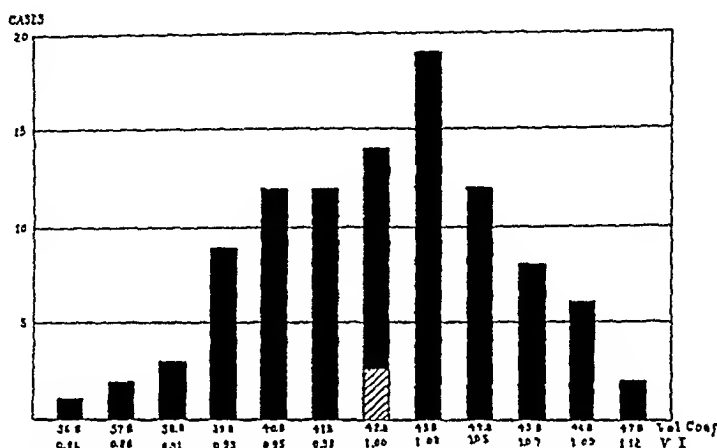


Fig. 6—Volume coefficients and volume indexes in one hundred women

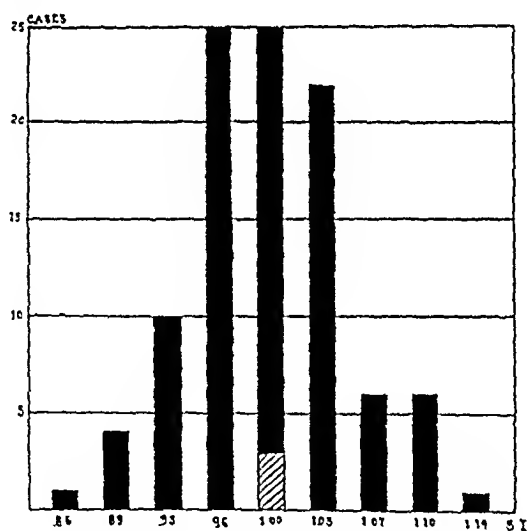


Fig. 7—Saturation indexes in one hundred women

90 per cent of the results correspond to volume indexes between 0.9 and 1.1. The lowest volume index was 0.86 and the highest was 1.11.

#### SATURATION INDEX

Haden<sup>7</sup> coined the term saturation index for the figure expressing the ratio between the concentration of hemoglobin per unit volume of cells in a particular subject and the average concentration of hemoglobin per unit volume of cells in normal subjects of the same sex and age group. It is most easily calculated by dividing the color index by the volume index.

Its clinical significance has not been fully worked out as yet. Our incomplete unpublished work shows that it is always low in anemia caused by chronic hemorrhage, either alone or complicating other types of anemia, and that it is within the normal range in pernicious anemia, aplastic anemia, hemolytic anemia and anemia caused by acute hemorrhage. The saturation index figure is probably never high.

Chart 7 shows that over 90 per cent of the results fall between 0.9 and 1.1. Fifty-six per cent of the women gave saturation indexes close to the average, that is, between 0.97 and 1.03. The extremes were 0.87 and 1.16.

#### METHOD OF CALCULATING RESULTS

It seems to us of value to give an illustration of our method of calculating results. For instance, in case number 100 our experimental data were as follows: 4.37 million red cells, 102.7 per cent hemoglobin and 1.58 cc of packed red cells in our special centrifuge tube from 3.95 cc of whole blood.

##### Calculations

$$\text{Total hemoglobin} = (102.7 \times 13.8) - 100 = 14.17 \text{ Gm per 100 cc}$$

The factor 13.8 is used because we adopted for our hemoglobin method the same standard figure as is used for the Van Slyke, the Dare, and most other hemoglobin methods (100 per cent meaning a content of 13.8 Gm per 100 cc).

$$\text{Hemoglobin coefficient} = 14.17 \times (5.00 - 4.37) = 16.22 \text{ Gm}$$

$$\text{Color index} = \text{per cent Hb} - \text{per cent red cells}$$

$$\text{Per cent Hb} = \frac{14.17 \times 100}{14.3} = 99.2 \text{ per cent}$$

The figure 14.3 is the average hemoglobin coefficient

$$\text{Per cent cells} = \frac{4.37 \times 100}{5.00} = 87.4 \text{ per cent}$$

$$\text{Therefore, the color index} = \frac{99.2}{87.4} = 1.13$$

$$\text{Total volume of cells} = (1.58 - 3.95) \times 100 = 40 \text{ cc}$$

$$\text{Volume coefficient} = (40 \times 5) - 4.37 = 45.77 \text{ cc}$$

$$\text{Volume index} = \text{cell volume per cent} - \text{per cent red cells}$$

$$\text{Cell volume per cent} = (40 \times 100) - 42.8 = 93.5 \text{ per cent}$$

The figure 42.8 is the average volume coefficient

$$\text{Volume index} = \frac{93.5}{87.4} = 1.07$$

$$\text{Saturation index} = \text{color index} - \text{volume index} = \frac{1.13}{1.07} = 1.06$$

For regular routine work the hemoglobin and volume coefficient would not be calculated. A set of tables which will greatly simplify the calculations is being prepared by one of us and will be published soon in the *Journal of Laboratory and Clinical Medicine*.

#### SUMMARY

1. The figures usually given for normal red cell counts in men (5 million) and in women (4.5 million) are incorrect. They never had a sound experimental basis.

2 The actual average red cell count in 100 women from 18 to 30 years of age was 4.8 million, 90 per cent of the cases falling between 4.3 and 5.3 million. In contrast to this, our previous work<sup>4</sup> showed an average count of 5.4 million in 137 men (19 to 30 years of age) with 90 per cent falling between 4.7 and 6.1 million.

3 The average total hemoglobin per one hundred cubic centimeters of blood in young women is 13.7 Gm. with 90 per cent of the results falling between 12 and 15.5 Gm. In men the average was 15.8 Gm. (not 13.8 Gm. as is commonly stated), and 90 per cent of the results fell between 14 and 18 Gm.

4 The average *hemoglobin coefficient*<sup>21</sup> in young women is 14.3 Gm. and in men 14.7 Gm. These are the figures that should be taken as 100 per cent hemoglobin in calculating color indexes of young adults.

5 The total volume of packed red cells per one hundred cubic centimeters of blood averages 41 cc. in women (90 per cent between 37 and 45) and 45 cc. in men (90 per cent between 40 and 50).

6 The average *volume coefficient*<sup>23</sup> in women is 42.8 cc., and in men is 41 cc. provided that our technic<sup>4</sup> is used. These are the figures that should be used as 100 per cent in calculating volume indexes. We cannot account for the slightly larger red cells in women, but the difference appears to be significant.

7 The various indexes (color, volume and saturation) will average 1.0 in normal young adults if they are properly calculated and are based on accurate estimations of cells, hemoglobin and cell volume. About 90 per cent of the results will fall between 0.9 and 1.1.

One must be cautious in interpreting results between 0.8 and 0.9 and between 1.1 and 1.2, because a few normal persons (up to 10 per cent) give indexes in these ranges in spite of careful technic and accurate methods. In all of our cases, of both men and women, we found only six indexes outside the range 0.85 to 1.15.

8 The standards proposed on the basis of our work (100 female and 137 male subjects) should be used by physicians until more extensive investigations are reported.

9 The literature relating to these observations in women has been reviewed, but it is unsatisfactory because complete data comparable to our own are given for only fifteen women from 18 to 30 years of age.

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<sup>23</sup> The terms hemoglobin coefficient and volume coefficient were suggested by us in a previous article (footnote 4).

# METABOLIC STUDIES IN THE TREATMENT OF POLYCYTHEMIA VERA WITH PHENYLHYDRAZINE \*

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Phenylhydrazine hydrochloride was used for the first time in the treatment of polycythemia vera in 1918 by Eppinger and Kloss<sup>1</sup>. They used the drug in four cases in which the number of erythrocytes was satisfactorily reduced, and the symptoms were relieved without apparent injurious effects on the patient. Others<sup>2</sup> on the continent have since reported their experiences. Owen<sup>3</sup> was the first in this country to record experience with this method, and he has more recently<sup>4</sup> amplified his previous report. Long,<sup>5</sup> and Brown and Giffin<sup>6</sup> have also attested its value.

So far as I know, quantitative metabolic studies have not been reported on patients with polycythemia vera during treatment with phenylhydrazine hydrochloride. Such studies not only should have academic interest, but should also furnish data by which the results of the treatment could be estimated.

The formula for phenylhydrazine is  $C_6H_5NH-NH_2$ . The drug and its compounds have been used extensively in the experimental production of anemia and in studying phases of hepatic injury. In 1885, Hoppe-Seyler<sup>7</sup> first employed the hydrochloride derivative in animal experimentation. He noted its blood-destroying qualities, which apparently were brought about by the reducing action of the drug on the hemoglobin. Acetyl phenylhydrazine was introduced into therapeutics

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\* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1926.

1 Eppinger, H., and Kloss, K. Zur Therapie der Polyzythämie, *Therap Monatsh* **32** 322, 1918.

2 Strasburger, J. Zur Behandlung der Polyzythämie *Therap Monatsh* **35** 777, 1921. Taschenberg, E. W. Ueber die Behandlung der Polyzythämie mit Phenylhydrazin, *Deutsche med Wchnschr* **2** 774, 1921.

3 Owen, Trevor. A Case of Polycythaemia Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazin, *Bull Johns Hopkins Hosp* **35** 258, 1924.

4 Owen, Trevor. The Treatment of Erythremia with Phenylhydrazin, *J A M A* **85** 2027 (Dec 26) 1925.

5 Long, P. H. Effect of Phenylhydrazin Derivatives in the Treatment of Polycythemia, *J Clin Investigation* **4** 315, 1926.

6 Brown, G. E., and Giffin, H. Z. Studies on Polycythemia Vera (Erythremia) During Treatment with Phenylhydrazin, *Arch Int Med* **38** 321 (Sept) 1926.

7 Hoppe-Seyler, Georg. Ueber die Wirkung des Phenylhydrazins auf den Organismus, *Ztschr f physiol Chem* **9** 34, 1885.

because of its antipyretic properties (hence the name pyrodine), but was soon abandoned when its hemolytic action was noted. In a case recorded by Renvers<sup>8</sup> there was a fall in erythrocytes from 4,000,000 to 2,800,000 in three days, with the administration of 0.5 Gm of the drug. The hemolytic action was confirmed by Frankel,<sup>9</sup> among others, who made a study on two dogs in which a fixed diet was used. He noted an increased excretion of nitrogen after subcutaneous injections of acetyl phenylhydrazine. He believed that this increased excretion of nitrogen was due to protoplasmic injury and to the decreased oxidation occurring in consequence of the destruction of blood.

Frankel, and later Tallquist,<sup>10</sup> noted the frequency of hepatic injury in pyrodine anemia. This occurs in the poisoning produced by hydrazine compounds generally, as shown by Wells,<sup>11</sup> although not to the same degree in all compounds, as shown by Bodansky.<sup>12</sup> The latter, while studying the hepatic injury produced by different hydrazine compounds, found extensive degeneration of the liver, marked hyperpigmentation of the spleen and extreme destruction of the red corpuscles in one dog following subcutaneous injections of phenylhydrazine hydrochloride. In another animal injections of acetyl phenylhydrazine produced marked anemia, but little destructive change could be demonstrated in the hepatic cells.

Von Roeder, quoted by Kuhnau,<sup>13</sup> found a marked increase in the leukocytes in rabbits receiving intraperitoneal injections of phenylhydrazine hydrochloride. Tallquist also observed this in his animals with pyrodine poisoning, the increase affecting chiefly the myeloblastic elements. He also found in a subsequent investigation on the same animal that larger and larger doses of the drug were needed to produce similar degrees of anemia. Morawitz and Pratt<sup>14</sup> ascribed this occurrence to increased resistance of the erythrocytes to hemolytic agents generally brought about as the response of the body to the toxic action of the drug.

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8 Renvers. Ueber Pyrocin, *Deutsche med Wchnschr* **15** 964, 1889.

9 Frankel, A. Ueber das Verhalten des Stoffwechsels bei Pyrocinvergiftung, *Ztschr f klin Med Supplement* **17** 239, 1890.

10 Tallquist, F. W. Ueber experimentelle Blutgriff-Anämien, Berlin, Hirschwald, 1900, pp 205.

11 Wells, H. G. The Pathological Anatomy of Hydrazine Poisoning, *J Exper Med* **10** 457, 1908.

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13 Kuhnau. Ueber das Verhalten des Stoffwechsels und der weissen Blutelemente bei Blutdissolution, *Deutsches Arch f klin Med* **58** 339, 1897.

14 Morawitz, P., and Pratt, J. Einige Beobachtungen bei experimentellen Anämien, *Munchen med Wchnschr* **2** 1817, 1908.

Samuely<sup>15</sup> reported the results of carefully conducted quantitative metabolic studies in experimental anemia using acetyl phenylhydrazine as one of his hemolytic agents. His data showed, among other things, a decline in the excretion of urea nitrogen from 84 to 71 per cent, while the excretion of ammonia increased correspondingly.

The available data<sup>16</sup> on the nitrogenous metabolism in cases of polycythemia vera in which a fixed diet was used indicate little change from the normal. There is an increase of uric acid of the whole blood which Isaacs<sup>17</sup> has attributed to an increase in the extruded nuclear material associated with increased formation of erythrocytes. There is usually an increase in the amino-acid content of the blood. Numerous workers have reported the occurrence of an increased basal metabolic rate, the increase seeming to be somewhat proportional to the erythrocytic content of the blood, although this is not always the case.

#### MATERIAL STUDIED AND METHODS EMPLOYED

This report embodies studies of the chemistry of blood and urine in four cases of polycythemia vera in which a reduction in erythrocytes and blood volume was affected by phenylhydrazine hydrochloride. A weighed diet or standard food portion was given each patient, the food values of which were computed from Atwater and Bryant's<sup>18</sup> tables. Unless otherwise stated, this diet daily consisted of 40 Gm of protein, 55 Gm of fat and 200 Gm of carbohydrate with a caloric value of 1,500, and may be considered a basal maintenance diet for the average adult patient at rest. The relatively low content of protein was prompted by the possibility of renal and hepatic injury being produced by the phenylhydrazine hydrochloride. The total twenty-four hour quantity of urine was saved, and toluene was added as a preservative. Attempts were made to secure uniform times of collecting the specimens, and for the most part this was accomplished. Blood for study was drawn by venipuncture from the median basilic vein at regular intervals before breakfast.

The following methods were used in the study of the urine: for total nitrogen, the Kjeldahl method, for urea nitrogen, the urease method for ammonia nitrogen, the Folin and Bell method, for creatine, creatinine

15 Samuely, Franz. Stoffwechseluntersuchungen bei experimenteller Anämie, *Deutsches Arch f klin Med* **89** 220, 1906.

16 Gordon, J M. Zur Kenntniss der Erythram, *Ztschr f klin med* **68** 1, 1909. Low, Josef, and Popper, Hugo. Beitrag zur Klinik der Polyzythämie, *Wien klin Wchnschr* **21** 357, 1908. Senator, H. Ueber Erythrozytosis (Polycythaemia rubra) Megalosplenica, *Ztschr f klin med* **60** 357, 1909.

17 Isaacs, Rafael. Pathologic Physiology of Polycythemia Vera, *Arch Int Med* **31** 289 (Feb) 1923.

18 Atwater, W O, and Bryant, A P. The Chemical Composition of American Food Materials, U S Department of Agriculture, Washington, Government Printing Office, 1906, Bull 28.

and uric acid, the Folin method. In the study of the blood, the methods used were the acid-hematin method of Haden for hemoglobin, Folin's methods for nonprotein nitrogen, creatinine, sugar, uric acid and amino-acids, the urease method for urea, van den Bergh's method for serum bilirubin, Van Slyke's method for carbon dioxide combining power, and Keith, Rowntree and Geraghty's dye method for blood volume. The fecal nitrogen was not determined, the total nitrogen was computed by adding 10 per cent of the food nitrogen to the urinary nitrogen.

Phenylhydrazine hydrochloride was given by mouth in an average dosage of 0.3 Gm daily. This dose was continued until the desired therapeutic effect had been obtained or had been approached, so that there was considerable variation in the total amount given in the different cases. The nitrogen content of the drug is too small to affect the general result.

The changes observed in the four cases studied are given in the tables accompanying the case reports. The daily changes are shown in the illustrations. In the tables the urinary changes are reported in terms of the daily average over a five day period. These cases are among those recently reported in a detailed clinical study by Brown and Giffin.<sup>6</sup> Complete studies could not be made in case 1 (Brown and Giffin, case 2), but I report the data obtained on four representative days during the course of treatment. In case 2 (Brown and Giffin, case 7) it was not possible to make studies before the administration of phenylhydrazine was started, but in case 4 (Brown and Giffin, case 4) a two day and in case 3 (Brown and Giffin, case 3) a five day control period was arranged.

#### REPORT OF CASES

**CASE 1**—The results of examination of the blood in a man, aged 56, were hemoglobin content, 29.4 Gm per hundred cubic centimeters of blood, erythrocytes, 8,530,000, relative viscosity, 12, total blood volume, 12,400 cc or 190 cc for each kilogram of body weight. The hematocrit revealed 72 per cent of erythrocytes. The spleen was palpable. The patient was given 64 Gm of phenylhydrazine over a period of sixteen days. Destruction of blood was marked, the hemoglobin being reduced to 9.5 Gm and the erythrocytes to 2,180,000, while the blood volume was reduced to 5,050 cc (table 1).

**CASE 2**—The condition of a man, aged 58, was diagnosed polycythemia vera although the erythrocytes numbered only 5,490,000. There was 19 Gm of hemoglobin per hundred cubic centimeters of blood, the total blood volume was 8,350 cc or 112 cc for each kilogram of body weight, and the relative viscosity of the whole blood was 10.5. The volume of erythrocytes was 50 per cent by hematocrit examination. The spleen was palpable. A total dose of 4.5 Gm was given over a period of fifteen days. The hemoglobin was reduced to 6.5 Gm per cent, the erythrocytes to 2,020,000 and the total blood volume to 6,150 cc. Five days elapsed after the phenylhydrazine was started before the study of the nitrogen partitions of the urine was begun (table 2 and chart 1).

**CASE 3**—A man, aged 43, had an erythrocyte count of 8,750,000 on admission to the hospital. The hemoglobin content was 27.4 Gm per hundred cubic centimeters of blood, and the whole blood volume was 13,350 cc. The relative

TABLE 1—The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera,  
(Patient a man, aged 56)

Date, 1923	Weight, Kg	Diet Gm			Urine										Blood																		
		Protein	Fat	Carbohydrate	Total Nitrogen, Gm	Urea Nitrogen, Gm	Ammonia Nitrogen, Gm	Creatinine Nitrogen, Gm	Creatinine Nitrogen, Gm	Uric Acid Nitrogen, Gm	Rest Nitrogen, Gm	Nitrogen Balance, Gm	Phenolsulphonophthalein, per Cent Retain in Two Hours	Volume, Cc	Erythrocytes, Millions	Hemoglobin, Gm per 100 Cc	Hematocrit, per Cent	Nonprotein Nitrogen, Mg	Urea Nitrogen, Mg	Creatinine Nitrogen, Mg	Uric Acid Nitrogen, Mg	Amino-Acid Nitrogen, Mg	Serum Bilirubin, Mg	Van den Bergh Direct Reaction	Minutes	One Hour	Two Hours	Phenol-tetrachlorophthalein in Serum, per Cent	Blood Sugar, Mg	Carbon Dioxide Combining Power, per Cent by Volume	Basal Metabolic Rate Du Bois Standard, per Cent	Phenylhydrazine, Gm	
4/16	61.4	40	55	200	7.30	—	—	—	—	—	—	—	—	12,100	836	220	29.4	32	34	0.97	0.87	7.1	0.9	0	3	0	—	—	—	—	—	—	—
4/28	63.5	40	55	200	8.60	—	—	—	—	—	—	—	—	11,100	497	208	34	30	47	0.80	0.71	10.3	2.4	0	1	0	—	—	—	—	—	—	—
5/6	—	40	55	200	10.00	—	—	—	—	—	—	—	—	8,750	497	208	34	30	47	0.80	1.20	11.3	3.4	0	3	0	—	—	—	—	—	—	—
5/15	61.5	40	55	200	15.00	—	—	—	—	—	—	—	—	5,050	328	125	26	24	49	1.40	1.30	7.3	4.3	0	3	0	—	—	—	—	—	—	—
5/20	61.4	40	55	200	12.00	—	—	—	—	—	—	—	—	—	220	9.5	26	24	49	1.40	0.87	8.9	0.9	0	3	0	—	—	—	—	—	—	—

TABLE 2—The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera  
(Patient a man, aged 58)

Date, 1923	Diet, Gm			Urine										Blood										Phenylhydrazine, Gm								
	Weight, Kg	Protein	Fat	Carbohydrate	Total Nitrogen, Gm	Urea and Ammonia Nitrogen, Gm	Urea, Gm	Creatinine Nitrogen, Gm	Creatinine Nitrogen, Gm	Urea Nitrogen, Gm	Uric Acid Nitrogen, Gm	Rest Nitrogen, Gm	Nitrogen Balance, Gm	Phenolsulphonophthalein, per Cent Return in Two Hours	Blood Volume, Cc	Erythrocytes, Millions	Hemoglobin, Gm per 100 Cc	Hematocrit, per Cent	Nonprotein Nitrogen, Mg	Urea Nitrogen, Mg	Creatinine Nitrogen, Mg	Uric Acid Nitrogen, Mg	Amino Acid Nitrogen, Mg		Serum Bilirubin, Mg	Van den Berg's Direct Reaction	Fifteen Minutes	One Hour	Two Hours	Carbon Dioxide Combining Power, per Cent by Volume	Basal Metabolic Rate Du Bois	
9/12-16/16	73.3	40	55	200	8.20	11.00	1.00	0.30	0.30	0.25	1.03	0.25	0.04	0.04	38.8	26.2	22.7	8.3	34	31	8	0.94	1.00	4.4	1.7	0	1	1	1	38	40	15
8/12-16/16	73.1	40	55	200	10.20	11.87	1.00	0.30	0.30	0.29	1.03	0.25	0.04	0.04	39.0	22.2	27.3	8.5	33	31	8	0.94	1.00	4.4	3.0	0	1	1	1	38	40	15
7/23/11	72.3	40	55	200	15.98	11.35	1.00	0.30	0.30	0.18	1.15	0.25	0.07	0.07	39.0	22.2	27.3	11.6	40	32	8	0.94	0.93	4.8	4.8	0	1	1	1	38	40	15
6/23/11	72.6	40	55	200	16.58	11.35	1.00	0.30	0.30	0.18	1.15	0.25	0.07	0.07	38.8	22.2	27.3	10.9	42	32	8	0.94	0.93	3.7	3.7	0	1	1	1	38	40	15
5/20-24/15	72.4	40	55	200	12.00	11.00	1.00	0.30	0.30	0.25	1.00	0.25	0.04	0.04	38.8	26.2	22.7	8.3	34	31	8	0.94	0.93	1.7	1.7	0	1	1	1	38	40	15
4/23/11	72.3	40	55	200	10.20	11.87	1.00	0.30	0.30	0.29	1.03	0.25	0.04	0.04	38.8	22.2	27.3	8.3	33	31	8	0.94	0.93	1.4	1.4	0	1	1	1	38	40	15
3/23/11	72.3	40	55	200	15.98	11.35	1.00	0.30	0.30	0.18	1.15	0.25	0.07	0.07	38.8	22.2	27.3	11.6	40	32	8	0.94	0.93	1.4	1.4	0	1	1	1	38	40	15
2/20-24/15	72.4	40	55	200	12.00	11.00	1.00	0.30	0.30	0.25	1.00	0.25	0.04	0.04	38.8	26.2	22.7	8.3	34	31	8	0.94	0.93	1.4	1.4	0	1	1	1	38	40	15
1/15	72.4	40	55	200	12.00	11.00	1.00	0.30	0.30	0.25	1.00	0.25	0.04	0.04	38.8	26.2	22.7	8.3	34	31	8	0.94	0.93	1.4	1.4	0	1	1	1	38	40	15

viscosity was 118. The spleen was enlarged, extending 13 cm below the costal margin. The diagnosis was polycythemia vera. The patient received 61 Gm of phenylhydrazine hydrochloride during a period of sixteen days. A marked decrease in the circulating blood volume in the hemoglobin and in the number of erythrocytes occurred. Marked icterus was seen at the height of erythrocytic destruction, and hemoglobinuria was demonstrated. The excretion of phenolsulphonphthalein decreased to 25 per cent in two hours, but later returned to normal (table 3, chart 2).

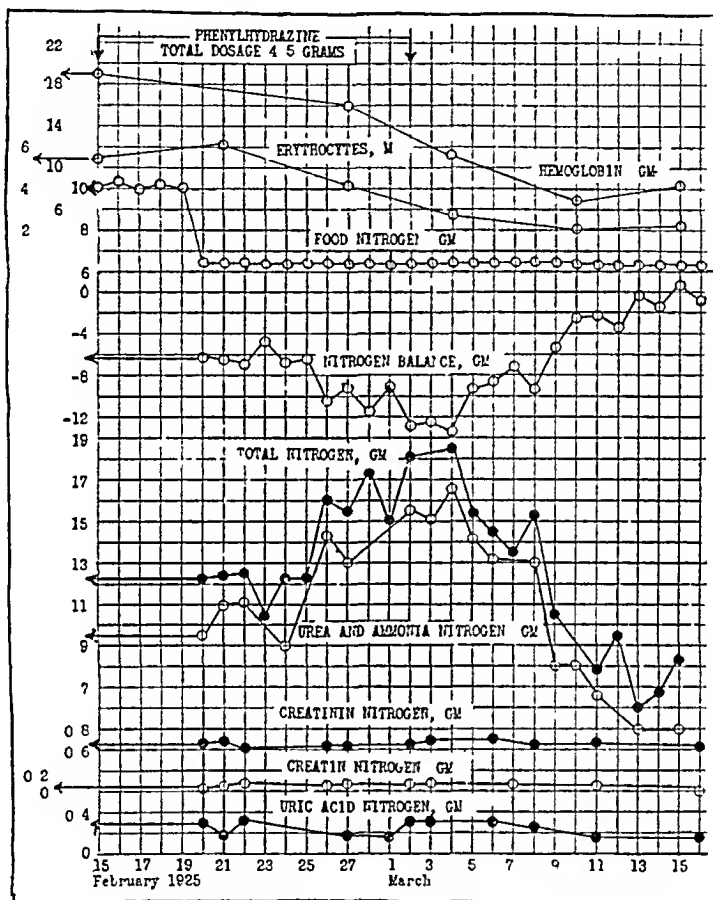


Chart 1—Effect of phenylhydrazine on the blood and the nitrogenous partition products in the urine in a case of polycythemia vera

CASE 4—In a woman, aged 31, the erythrocytes numbered 6,890,000, the hemoglobin content was 23.3 Gm per hundred cubic centimeters of blood, and the whole blood volume was 7,700 cc or 167 cc for each kilogram of body weight. The spleen extended 4 cm below the costal margin. A total dose of 35 Gm of phenylhydrazine was given during a period of eleven days. The reduction in hemoglobin and erythrocytes and blood volume was definite. On one occasion, during the time of apparent maximal destruction of erythrocytes, the patient vomited blood-streaked material. The urine contained macroscopic blood, and slight jaundice developed. Moderate albuminuria was also present (table 4 and chart 3).

TABLE 3—The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera

(Patient a man, aged 43)

Date, 1925	Weight, Kg	Diet, Gm			Urine										Blood																						
		Protein	Fat	Carbohydrate	Total Nitrogen, Gm	Urea Nitrogen, Gm	Ammonia Nitrogen, Gm	Creatinine Nitrogen, Gm	Creatine Nitrogen, Gm	Uric Acid Nitrogen, Gm	Rest Nitrogen, Gm	Nitrogen Balance, Gm	Urinary Pigment Calculated as Gms, Hemoglobin	Phenolsulphonphthalein, per Cent Return in Two Hours	Blood Volume, Cc	Erythrocytes, Millions	Hemoglobin, Gm per 100 Cc	Hematocrit, per Cent	Blood	Total Nitrogen, Gm	Plasma	Nonprotein Nitrogen, Mg	Urea Nitrogen, Mg	Creatinine Nitrogen, Mg	Uric Acid Nitrogen, Mg	Amino-Acid Nitrogen, Mg	Serum Bilirubin, Mg	Van den Bergh Direct Reaction	Fifteen Minutes	Thirty Minutes	Sixty Minutes	Normal	One Hour	Carbon Dioxide Combining Power, per Cent by Volume	Basal Metabolic Rate Du Bois	Phenylhydrazine, Gm	
7/27-7/31	69.7	40	60	300	7.4	5.9	0.26	0.38	0.05	0.28	0.0	—	1.71	69	13,350	575	27.4	17	1.07	0.60	1.67	60	13	57	13	95	1.5	9.7	1.7	0	5	0	0	47	+21	0	
8/1-8/5	69.2	40	60	300	6.81	5.80	0.26	0.38	0.05	0.22	0.11	1.06	0.92	—	10,600	744	24.4	63	1.67	0.97	42	14	0.74	19	9.5	—	—	—	—	—	—	—	—	—	—	—	18
8/6-8/10	65.8	37	60	200	10.32	8.20	0.67	0.43	0.05	0.22	0.75	5.00	1.36	—	8,600	628	24.0	60	1.67	1.30	36	28	0.56	1.3	7.2	6.2	—	—	—	—	—	—	—	—	—	18	
8/11-8/15	64.2	40	60	200	13.03	11.04	0.41	0.23	0.16	0.18	0.95	10.15	1.63	—	—	5,960	596	14.0	59	1.20	1.30	99	81	1.26	1.6	8.8	4.9	0	10	1	0	—	—	—	0		
8/16-8/20	60.9	40	60	200	16.52	13.36	0.60	0.20	0.11	0.25	1.01	16.32	2.69	25	3,950	1,255	8.6	27	2.40	1.51	99	95	1.19	1.6	6.6	3.7	0	10	1	0	—	—	—	0			
8/21-8/25	61.2	40	60	300	8.18	6.49	0.60	0.26	0.05	0.20	0.58	2.42	0.90	25	—	5,500	2,033	8.6	25	2.40	1.51	139	95	1.19	1.7	5.9	1.9	0	5	0	0	—	—	—	0		
8/26-8/30	67.1	40	60	300	5.31	3.80	0.38	0.26	0.02	0.19	0.99	+	0.80	55	5,500	1,738	5.7	51	2.40	1.51	45	21	0.56	1.7	5.9	1.9	0	5	0	0	—	—	—	0			

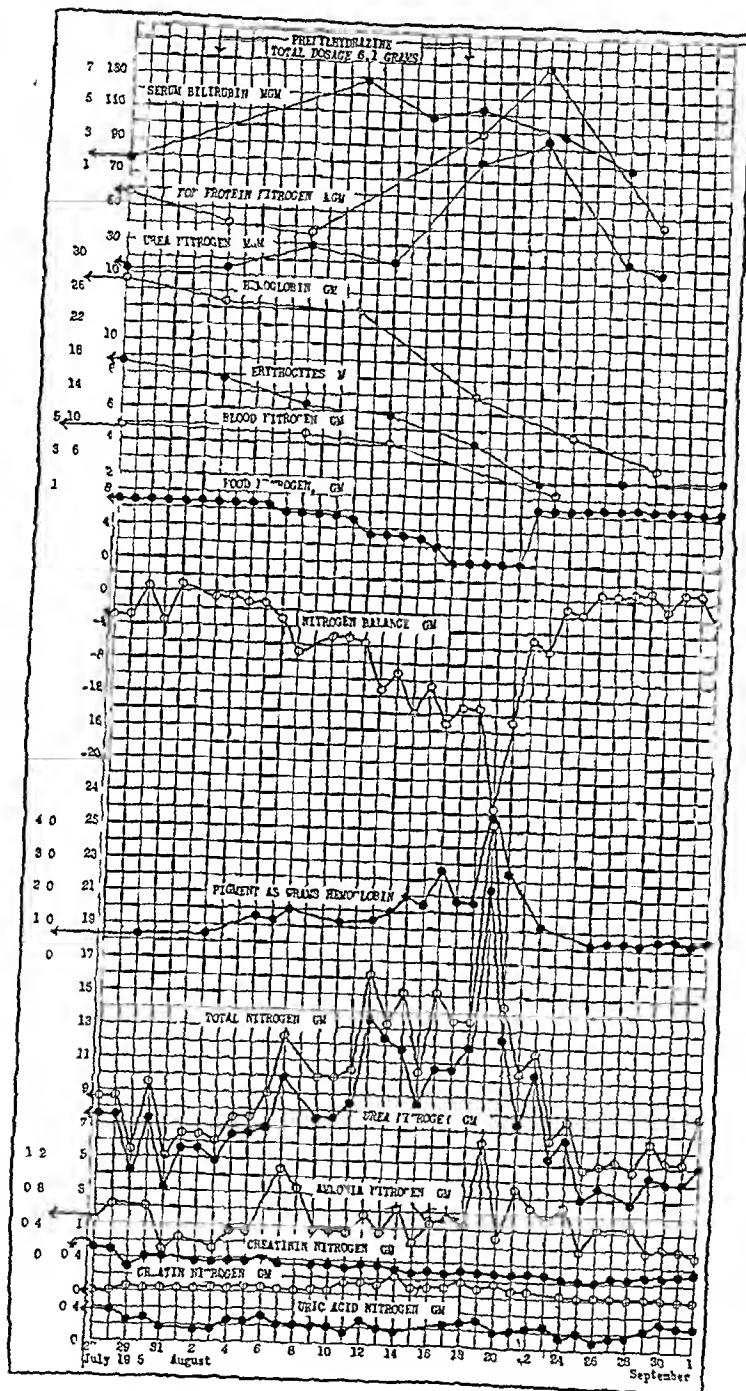


Chart 2—Effect of phenylhydrazine on the blood and the nitrogenous partition products in the urine in a case of polycythemia vera



## RESULTS

*Urinary Changes*—Usually about seven days elapse following the administration of phenylhydrazine before the evidences of blood destruction are manifest. At this time increased excretion of nitrogen is found, further increase being rapid and progressive as the treatment is continued. The excretion of nitrogen is maintained at a high level for a number of days after withdrawal of the drug and then rapidly declines.

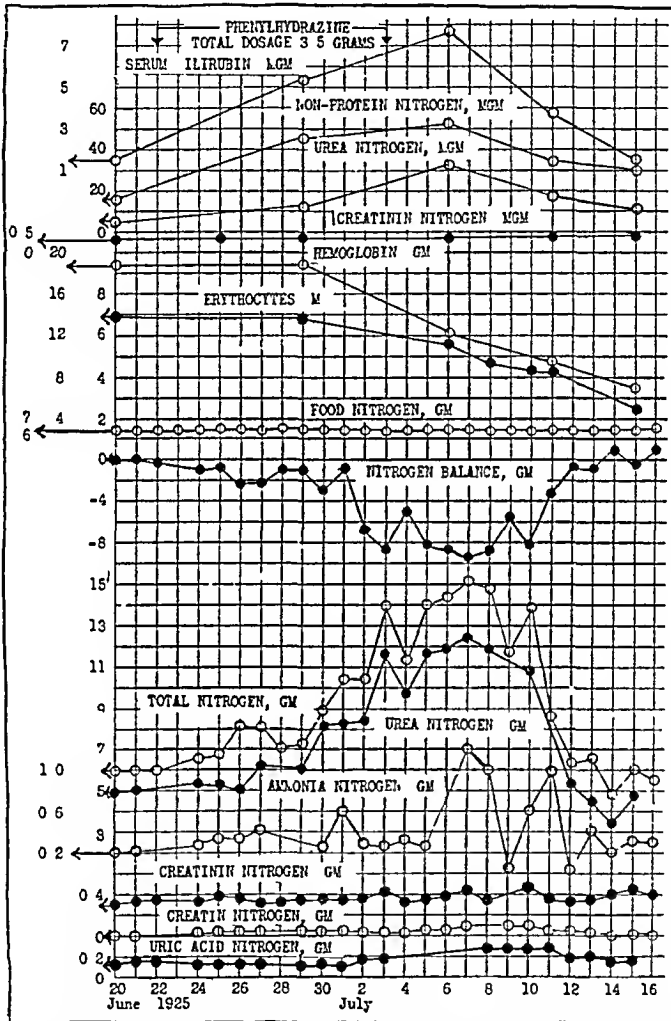


Chart 3—Effect of phenylhydrazine on the blood and the nitrogenous partition products in the urine in a case of polycythemia vera

to the initial level. The increase in nitrogen output is most marked during the period of greatest decrease in erythrocyte and hemoglobin content of the blood.

In case 3 the total nitrogen increased from a daily level of 7.47 to 25 Gm. After the drug was withdrawn, there was a continued daily negative nitrogen balance for several days, then the urinary nitrogen declined to 5.3 Gm, which, compared to the initial level of 7.47 Gm, indi-

cated slight nitrogen retention. During the time of maximal destruction of erythrocytes a daily negative nitrogen balance amounting to 12.15 Gm or more occurred, and a total negative balance of 100 Gm or more. A loss of weight occurred during the time of maximal destruction of erythrocytes, but this weight was rapidly regained after discontinuance of the drug. In all cases the estimated destruction of blood was more than sufficient to account for the negative nitrogen balance.

The urea nitrogen rose to a high level after the administration of phenylhydrazine. It gradually decreased to a normal level after the drug had been stopped. The variation in urea reflected accurately the variation in total nitrogen.

The excretion of ammonia showed variations which were for the most part within normal limits. On a few occasions values were obtained indicating excretion of ammonia amounting to 10 per cent of the total. However, the absence of significant fluctuations together with the relative constancy of the carbon dioxide capacity excluded any significant effect of the phenylhydrazine on the acid-base balance of the body.

In general, the creatinine showed little variation from normal values. If the creatinine which is eliminated is an index of destruction of living protoplasm, then such tissue is not involved in the protein destruction produced by the phenylhydrazine hydrochloride as used in these cases. In case 3 there was a slight relative decrease in the preformed creatinine excreted, although the total was unchanged. After nitrogen equilibrium had been reestablished subsequent to withdrawal of the drug, the total decreased to the level of the preformed creatinine.

Slight creatinuria was frequently present during the time of the administration of the phenylhydrazine hydrochloride. This rapidly disappeared after the drug was stopped. Cathcart<sup>19</sup> showed that the carbohydrate metabolism is concerned in some way with the conversion of creatine to creatinine. Greene, Connor<sup>20</sup> and I did not find evidence of a disturbance in the carbohydrate metabolism in these cases. Another and simpler explanation may be found in the fact that the erythrocyte contains practically all the circulating creatine<sup>21</sup>. In the disintegration of the corpuscle, creatine escapes in such amounts that small quantities appear in the urine.

Since the diet was not absolutely purin-free, the estimations of uric acid hold interest from their qualitative rather than from their quantitative value. For the most part the excretion of uric acid exhibited values within the normal range, from which the conclusion is made that

19 Cathcart, E. P. Metabolism During Starvation, *J. Physiol.* **35** 500, 1907.

20 Greene, C. H., and Connor, H. M. Diseases of the Liver. V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System. *Arch. Int. Med.* **38** 167 (Aug.) 1926.

21 Hunter, Andrew, and Campbell, W. R. The Amount and the Distribution of Creatinine and Creatine in Normal Human Blood, *J. Biol. Chem.* **33** 169, 1918.

so far as the excretion of uric acid is an index of endogenous metabolism, this was not seriously deranged by the administration of phenylhydrazine.

The urine of patients taking phenylhydrazine is dark brown or mahogany. Hoppe-Seyler attributed this color to a pigment produced by the action of phenylhydrazine on hemoglobin. He showed its occurrence *in vitro*, but neither he nor subsequent investigators have been able to identify the supposed pigment with any of the usual hemoglobin derivatives. C. H. Greene quantitated this coloring matter, using an acid hematin solution as the standard. The results are shown in table 3 and chart 2 (case 3) in which the total pigment was calculated as grams of hemoglobin.

*Changes in the Blood*—During the administration of phenylhydrazine hydrochloride, there was a decrease in the total nitrogen of the blood (table 3 and chart 2) paralleling the reduction in percentage of corpuscles in such cases. The decrease in the total nitrogen of the blood must be referred to the decrease in erythrocytes and directly related to this decreased hematocrit value, since there was not a marked change in the nitrogen content of the plasma and corpuscles when they were taken separately.

The nonprotein nitrogen and the urea showed definite increases which paralleled the amounts of these substances eliminated in the urine and returned to normal as the excess of nitrogen was excreted.

The blood urea showed the most marked increase of the nitrogenous contents and accounted well for the increased nonprotein nitrogen. Such increases were of moderate degree, except that in case 3 an increase in the urea nitrogen to 95 mg. occurred. At this time the excretion of phenolsulphonphthalein was decreased to 25 per cent in two hours. The response of the patient to eliminative procedures was prompt, and later tests indicated that permanent impairment of renal function had not occurred.

The creatinine nitrogen increased from 0.56 to 1.26 mg. in case 3, in which there were direct evidences of renal impairment. In the other cases studied evidence of gross departure from the initial values was not found.

The uric acid content of the blood did not change markedly from the initial levels. For the most part the values obtained were consistently in the upper limits of normal.

The amino-acid nitrogen of the blood is increased in cases of polycythemia. During the administration of phenylhydrazine, the amino-acid gradually fell to normal values.

The serum bilirubin content in cases of polycythemia vera is within normal limits. Shortly after the administration of phenylhydrazine was begun, bilirubinemia occurred, the maximal values of which were obtained at the time of apparent maximal destruction of erythrocytes.

Daily determinations of the serum bilirubin were not attempted, but there was a marked parallelism between the curves of serum bilirubin and nitrogen excreted in the urine. It is likely that the changes in the serum bilirubin precede somewhat the changes in the excretion of nitrogen, but definite evidence of this was not obtained.

As indicated in the reports of cases, clinical icterus developed during the course of the action of the drug. However, the van den Beigh reaction remained indirect during the time of the most marked changes. The reaction with the Gmelin test for bile in the urine did not demonstrate its presence.

*Fructose Tolerance Test*—Bodansky has emphasized the changes in the fructose tolerance in dogs after toxic doses of phenylhydrazine and its derivatives. He considered the occurrence of hypoglycemia as indicative of the extent of hepatic injury. There was no change in the fasting blood sugar level in any of the cases studied, and the fructose tolerance did not change as a result of the administration of phenylhydrazine hydrochloride.

*Phenoltetrachlorophthalein Test*—The results of the phenoltetrachlorophthalein test of Rowntree and Rosenthal were used in some of these cases as an index to possible hepatic injury. Negative results were obtained throughout.

*Basal Metabolic Rate*—Characteristic changes were not observed in the heat exchange as indicated by the basal metabolic rate during the course of phenylhydrazine action. In cases 2 and 4 slight decreases were noted, but these were not considered significant. In general, it would appear that the heightened nitrogen catabolism did not significantly affect the transfer of energy.

#### COMMENT

The metabolic changes accompanying the therapeutic use of phenylhydrazine are as striking as the clinical effects. The origin of bile pigments from hemoglobin and the metabolic relationship between the destruction of hemoglobin and the formation of bilirubin are recognized. In the cases here reported this relationship is emphasized further by the appearance of a bilirubinemia which apparently corresponds roughly in degree with the intensity of the corpuscular destruction. The serum bilirubin can be used as a guide to the therapeutic action of the drug.

The bilirubinemia is of hemolytic origin and not due to obstruction, so that bilirubin does not appear in the urine, at least not in appreciable quantities. The urine, however, contains an unidentified brown pigment first described by Hoppe-Seyler, which apparently is a product of hemoglobin destruction. It appears in increasing amounts as the destruction of erythrocytes continues and disappears when the drug is with-

drawn This pigment likewise can be demonstrated in the blood serum when the changes in the urine are most marked Like Frankel, I have been unable to demonstrate the presence of methemoglobin or hematin in the blood or urine Neither have I been able to obtain positive tests for para-amino phenol, which Young <sup>22</sup> and others have demonstrated in cases of poisoning by aniline and acetanilid

Urinalysis showed an increase in the urobilin and urobilinogen excreted during the period of drug action The fate of the pigment moiety of the hemoglobin cannot be finally established in these experiments, since the excess bilirubin formed from destroyed erythrocytes would be excreted in the bile, and the latter could not be studied The increase in the urobilin and urobilinogen in the urine furnishes further evidence, even though indirect, of the presence of such an excess of bile pigment in the intestine

The changes in the urinary nitrogen apparently suffice to explain the fate of the protein moiety of the corpuscles and the hemoglobin molecule The daily excretion of creatinine and uric acid in the urine did not change significantly during the period of administration of the drug According to the current theories of protein metabolism, this would indicate an unchanged or normal total tissue metabolism Boothby and his collaborators<sup>23</sup> have applied this hypothesis in explaining effects of the administration of thyroxin in producing catabolism of stored or deposited protein Following the administration of phenylhydrazine to patients on a constant protein intake, there was a striking increase in the total nitrogen excreted in the urine This increase can be explained almost wholly by an increase in the elimination of urea nitrogen Frankel considered that the increased excretion of nitrogen observed in animals after the administration of acetyl phenylhydrazine was evidence of general tissue injury In view of the incomplete nature of his studies, this conclusion is not convincing In the cases here reported the accompanying evidence of destruction of erythrocytes and the constant endogenous metabolism indicate that the increased excretion of urea depends on the destruction of the proteins of the corpuscles The loss of nitrogen from the blood, whether calculated from the changes in the total blood volume or the total hemoglobin, was sufficient in all cases to account for all the excess of nitrogen appearing in the urine

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22 Young, A G Toxicological Studies of Anilin and Anilin Compounds II Hematological Studies of Anilin Poisoning, *J Pharmacol & Exper Therap* **27** 125 1926 Young, A G, and Wilson, J A Toxicological and Hematological Studies of Acetanilid Poisoning, *J Pharmacol & Exper Therap* **27** 133, 1926

23 Boothby, W M, Sandiford, Irene, Sandiford, Kathleen, and Slosse, Jean The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects I A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, *Tr A Am Phys* **40** 195, 1925, Ergeber, d *Physiol* **24** 728, 1925

Mild albuminuria, and later hemoglobinuria, followed by hematuria was observed in some of the cases. These changes have been recognized previously, and Frankel describes similar effects from acetyl phenylhydrazine. He ascribed them primarily to the destruction of erythrocytes rather than to primary renal injury. In three of the cases of the present series there was no reduction in the phenolsulphonphthalein output or increase in the blood creatinine, however, there was a marked rise in the nonprotein nitrogen and urea content of the blood, which varied with the changes in the urinary nitrogen. It seems probable, as with the serum bilirubin, that the rise in the blood urea is due to hemoglobin catabolism at a rate in excess of the excretory power of the organism. In consequence there was a temporary flooding of the kidney with urea and retention of the excess which determined the changes in the blood stream. Similar although less marked changes have been reported in normal persons after a heavy meat meal or a high protein diet. Boothby and his collaborators also report a slight to moderate increase in the blood urea after the administration of thyroxin accompanying the mobilization of the deposit protein, the retention varied in different cases apparently according to the relative ability of the kidneys to eliminate as fast as the protein was deaminized.

The greater part of the retained urea is apparently the effect of renal flooding. A slight degree of primary renal injury cannot be excluded. In case 3, in which an excessive dose of the drug was used, temporary renal insufficiency was produced. The excretion of phenolsulphonphthalein decreased from 65 to 25 per cent, the blood creatinine nitrogen increased from 0.56 to 1.26 mg, and the blood urea nitrogen rose to 95 mg. The renal insufficiency was temporary, and normal function was quickly restored. Baker and Dodds<sup>24</sup> have recently emphasized the action of hemoglobin on the kidney. Such an effect may serve to explain the observed renal changes in view of the hemoglobinuria in this case.

The toxic action of hydrazine, phenylhydrazine and allied substances has been emphasized by all who have studied these compounds. Changes in the carbohydrate metabolism have been especially emphasized as an index to such toxic action on the liver. No changes in either the fructose tolerance or the fasting blood sugar level were observed in the cases reported in this article.

Cirrhosis is recognized as a complication of polycythemia vera<sup>25</sup>. I have seen one case in which there was slight retention of dye before treatment, suggesting the initial presence of some cirrhotic changes, in no case did the retention of dye increase in consequence of treatment.

<sup>24</sup> Baker, B. L., and Dodds, E. G. Obstruction of Renal Tubules During Excretion of Hemoglobin. *Brit. J. Exper. Path.* 6: 247, 1925.

<sup>25</sup> Levi, Ernst. Ueber die Ursache der Leber Cirrhose beim Polycythämie, *Ztschr. f. klin. Med.* 100: 777, 1924.

On the basis of the metabolic changes observed, one may conclude that the action of therapeutic doses of phenylhydrazine is limited largely to the destruction of erythrocytes with a resultant increase in the products of hemoglobin catabolism. Renal irritation may follow too large doses, but serious renal or hepatic injury was not observed.

#### SUMMARY

Patients with polycythemia vera, on a fixed diet, showed a negative nitrogen balance during the period of erythrocytic disintegration brought about by the administration of phenylhydrazine. An increased elimination of nitrogen of the urine in the form of urea occurred. The other nitrogen fractions of the urine were only slightly changed.

The total blood volume, hemoglobin and hematocrit were reduced. The total blood nitrogen was decreased. The nonprotein nitrogen of the blood was increased. The urea fraction accounted for most of this increase and is attributable to the production of urea in excess of the eliminative ability of the kidneys. Primary renal injury as a result of the administration of phenylhydrazine cannot be excluded. The amino-acid nitrogen of the blood was decreased. The creatinine and uric acid were only slightly changed.

The serum bilirubin was increased, with the occurrence of slight icterus. The van den Bergh reaction remained indirect throughout. An increase in urinary pigment coincided with the bilirubinemia. A change in carbohydrate metabolism was not demonstrated. Serious renal or hepatic injury was not observed. Characteristic changes in the heat exchange, as indicated by the basal metabolic rate, were not observed.

# STUDIES IN ACROMEGALY

## IV THE BASAL METABOLISM \*

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AND

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BOSTON

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SUMMARY AND CONCLUSIONS

In a preceding paper in this series by one of us (Davidoff) which deals with the anamnesis and symptomatology of acromegaly as recorded in 100 personally observed cases, a brief statement was made concerning the influence of the malady on the basal metabolic rate (B M R<sup>1</sup>). It is proposed herein to discuss this matter more fully for it is generally assumed that the thyroid is the organ exclusively concerned in the regulation of tissue combustion.

One may dismiss from consideration the many and often painstaking studies of the chemical pathology of acromegaly from the time of Schiff's article in 1897<sup>2</sup> to that by Medigreceanu and Kristeller<sup>3</sup> in 1911. These early investigations tended to show that there is a retention of calcium and phosphorus in the disease, but the recorded observations were in large part contradictory. The studies were often complicated by the injection of inactive extracts or by the feeding of pituitary substance.

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\* From the Surgical Service of the Peter Bent Brigham Hospital. The preceding papers in this series have been: I Bailey and Davidoff, Concerning the microscopic structure of the hypophysis cerebri in acromegaly, *Am J Path* 1, 185-207, 1925; II Davidoff, Historical Note; III Davidoff, The Anamnesis and Symptomatology of One Hundred Cases, *Endocrinology* 10, 453, 1926.

1 For purposes of abbreviation these initials will be largely used to signify the basal metabolic rate in the succeeding pages.

2 Schiff, A, Hypophysis und Thyreoidea in ihrer Einwirkung auf den menschlichen Stoffwechsel, *Wien klin Wchnschr* 10, 277, 1897.

3 Medigreceanu, F, and Kristeller, L, General Metabolism with Special Reference to Mineral Metabolism in a Patient with Acromegaly Complicated with Glycosuria, *J Biol Chem* 9, 109, 1911.

in days when it was not appreciated that the anterior lobe principle is largely if not wholly destroyed in the stomach. Moreover, the tendency of the disease to undergo periods of varying activity or possibly to reach a permanently inactive stage was not then taken into consideration.

It was not until the principle of indirect calorimetry in the estimation of metabolism came to be introduced, largely as an outcome of the studies by Magnus-Levy, that the subject came to rest on its modern basis. In one of his earlier articles (1897) dealing primarily with the thyroid, the following statement was made <sup>4</sup>

In conclusion one more observation may be made concerning acromegaly. Virchow has already called attention to the similarity in the histologic character of the hypophysis and the thyroid gland, and today there is a great tendency to attribute to the hypophysis a rôle in acromegaly similar to that which the thyroid plays in Basedow's disease, and to treat that disease as the various disorders of the thyroid are treated, with organic extract (hypophysis, etc.). Certain, though of course not constant, symptoms of acromegaly resemble very much those of Basedow's disease: cardiac hypertrophy, exophthalmos, tachycardia, profuse sweats, copious urinary secretion, the appearance of polyphagia, glycosuria, and true diabetes. A combination of both diseases appeared to be present in a case recently studied at postmortem. In another case of acromegaly which was under my observation for a long while (hypophysis tablets without result), I also found continually an elevation of the gaseous exchange similar to the elevation found in Basedow's disease. A 52-year-old woman, of small stature, in an average of 12 experiments, used 270 ccm O<sub>2</sub>, 220.8 ccm CO<sub>2</sub>, i. e., with 52 Kg 5.19 ccm O<sub>2</sub>, 4.25 ccm CO<sub>2</sub> per kilo.

These results, which, to be sure, do not agree with those given by Schiff in a case of acromegaly with symptoms of myxedema [*sic*] and a "retarded" metabolism, in any event invite renewed study of the metabolism and gaseous exchange in acromegaly.

Ten years later (1907), the statement was briefly repeated by Magnus-Levy in his section in van Noorden's "Handbuch," and since then the assumption that the thyroid is wholly responsible for the high metabolic rate occasionally seen in acromegaly has gained almost universal credence. But in these intervening years we have learned much that is new about this protean disease, and the question may therefore deserve reconsideration even though it may not be possible to answer it with finality.

Previous to 1909, the distinction between *hyperpituitarism* and *hypopituitarism* was not well understood, or at least not fully emphasized. Many cases had come to be reported in the literature as ones of "pituitary tumor without acromegaly," and their possible relationship to what was known as adiposogenital dystrophy had been suggested, but it was not suspected, apparently, that these peculiar syndromes represented states the reverse of acromegaly. This was first made evident by

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<sup>4</sup> Magnus-Levy, A. Untersuchungen zur Schilddrüsfrage, Ztschr f klin Med **33** 269, 1897, Der Stoffwechsel bei Erkrankungen einiger Drüsen ohne Ausführungsgang, in Van Noorden Handbuch der Pathologie des Stoffwechsels, ed 2, 1907, vol 2, p 350.

the disclosure that an experimental hypophysectomy was likely to cause similar symptoms, namely adiposity, lethargy, subnormal temperature, sexual dystrophy and so on—symptoms which must therefore be caused from glandular deficiency. The experiments by Crowe, Cushing and Homans<sup>5</sup> which first made this clear were soon followed by Aschner's report<sup>6</sup> in which the influence of an hypophysectomy on the retardation of growth when it is performed on a young animal was first strikingly shown.

Although it was evident from their symptoms that these experimentally hypophysectomized animals must have a lowered tissue combustion, proof of this was first obtained in 1912 by Benedict and Homans<sup>7</sup>. Their painstaking studies which were carried out in the Carnegie Nutrition Laboratory showed a marked lowering of the metabolism of animals in a state of experimental hypopituitarism.

In the following year, 1913, on the opening of the Brigham Hospital, a laboratory under the direction of W. M. Boothby was equipped for the special purpose of investigating the metabolism of the ductless gland disorders. It was soon observed, in correspondence with the observations of Benedict and Homans, that patients with evident hypopituitarism showed on the whole a subnormal metabolic rate, whereas in the patients with acromegaly, as Magnus-Levy had long before pointed out, it was often considerably increased. The determinations for metabolism on the pituitary cases, however, in both this clinic and elsewhere, came to be subordinated to the intensive study of the metabolic rate in hyperthyroidism, for the latter proved to be more immediately of practical value not only as an indication of the activity of the thyroid disease, but also as a check on the effects of therapeutic measures, surgical or otherwise, employed to control it. Boothby's subsequent continuance of these studies at the Mayo Clinic led him to say in 1921<sup>8</sup>:

The possible increased metabolic rate in active acromegaly, and the decreased rate in the syndrome known as hypopituitarism, suggest that alterations in the activity of the pituitary gland may change the metabolic level. There is, however, as yet little evidence that the secretion of any part of the pituitary gland is concerned with the normal rate of cellular combustion in the sense that it acts as a calorogenic agency.

These two sentences, if we understand them correctly, seem to be somewhat contradictory unless they carry the implication that the hypo-

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5 Crowe, S. J., Cushing, H., and Homans, J. Experimental Hypophysectomy, *Bull. Johns Hopkins Hosp.* **21**, 127, 1910.

6 Aschner, B. Ueber die Funktion der Hypophyse, *Arch. f. d. ges. Physiol.* **146**, 1, 1912.

7 Benedict, F. G., and Homans, J. The Metabolism of the Hypophysectomized Dog, *J. M. Research*, **25**, 409, 1912.

8 Boothby, W. M. The Basal Metabolic Rate in Hyperthyroidism, *J. A. M. A.* **77**, 252 (July 23), 1921.

physis can act only indirectly as a calorigenic agent through the mediation of the thyroid. But even this, if it can be proved, would be important to know.

#### THE METABOLIC RATE IN ACROMEGALY AND HYPOPITUITARISM

The observations on metabolism which form the basis of our present article were made on seventy-two of the one hundred cases of acromegaly in the Bingham Hospital records up to Aug 1, 1926. Of these seventy-two patients, forty-nine showed the rate to be above normal, varying from +2 per cent to +61 per cent (average +18.6 per cent). Eliminating all the cases with a rate below +10 per cent as within the limits of normal, there remain thirty-two cases in which the average was +26 per cent. In twenty-three patients the rate was below normal, ranging from -1 per cent to -17 per cent (average -8.3 per cent). Only six of these twenty-three cases, however, showed a rate lower than -10 per cent: one -12 per cent, one -13 per cent, two -14 per cent, one -16 per cent and one -17 per cent.<sup>9</sup>

Although we are primarily concerned with the metabolism of acromegaly, it will be not amiss to contrast the figures given in the foregoing with the determinations for cases of pituitary insufficiency. In so doing, we will include only studies made on patients with hypopituitarism due to hypophysial adenomas which were histologically verified either at operation or at autopsy. We may thus avoid the complexities which are so often allowed to enter into the discussion of these subjects from the inclusion of a great variety of cases which are merely suspected of being pituitary cases.

Of the several hundred examples of clinical hypopituitarism which occur in the Bingham Hospital records, there are 107 with histologically verified chromophobe adenomas in which dependable metabolism determinations were also made. The average rate was -14 per cent. Only four of the patients had a registration above zero: namely +3 per cent, +5 per cent, +10 per cent and +11 per cent. Seventy-one, or 66.3 per cent, had a rate below -10 per cent with an average of -19.3 per cent, forty-six fell between -10 per cent to -20 per cent, twenty-one fell between -20 per cent and -30 per cent, four fell below -30 per cent, the lowest being -36 per cent.

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9 These determinations have been based on the surface area as determined by the method of DuBois and on the standard formulated by him. In pituitary disorders, however, we are dealing oftentimes with bizarre persons—short, fat people with small extremities, and overgrown people with hypertrophied extremities. Hence the relation of the body surface to stature and weight may differ considerably from the average normal. It is possible, therefore, that the B. M. R. for pituitary cases, to be comparable, should be calculated from a modified formula.

These two sets of figures may be compared with those cited by Boothby and Sandiford<sup>10</sup> in a comprehensive analysis of their observations on metabolism made up to 1922 on conditions of all kinds at the Mayo Clinic. Their table includes determinations on thirty patients with acromegaly and on fifty-eight cases of so-called hypopituitarism. Of the thirty patients with acromegaly, 6.6 per cent showed a B M R below  $-10$ , 43 per cent fell in normal limits, and 50 per cent were above  $+10$ , half of these being above  $+20$  per cent. On the other hand, of the fifty-eight cases of hypopituitarism, 53.5 per cent were below  $-10$ , 34.5 per cent fell within normal limits, and only 12 per cent were above  $+10$  per cent.

For ease of comparison with our own determinations, these figures may be expressed as follows:

- (a) Hyperpituitarism (Acromegaly) with Chromophile adenoma  
Our figures show 45.8% of seventy-two cases above  $+10\%$   
Boothby's figures show 50.0% of thirty cases above  $+10\%$
- (b) Hypopituitarism with Chromophobe Adenoma  
Our figures show 66.3% of 107 verified cases below  $-10\%$   
Boothby's figures show 53.5% of 58 verified(?) cases below  $-10\%$

The figures from the two clinics are therefore essentially in agreement. The main difference appears to lie in the interpretation of the data. Whatever this may be, one may say with justifiable conviction (1) that acromegaly, which is no less unmistakably a disorder due to hyperpituitarism than exophthalmic goiter is due to hyperthyroidism, often shows an elevated basal metabolic rate, (2) that the syndrome of pituitary insufficiency like myxedema shows a consistently lowered basal metabolic rate, (3) that the extreme variations in the rate, in accord with Magnus-Levy's statement already quoted, prove much greater in the disorders of the thyroid than in those of the hypophysis.

#### ACROMEGALY AND GOITER

The question now before us is whether a coincidental hyperthyroidism, either primary or secondary, is responsible for the increased rate often seen in acromegaly. As is well known, hyperthyroidism is not accompanied by any gross secondary changes in the hypophysis. Acromegaly, on the other hand, is commonly associated with a goiter of variable size which is often much larger than that which could be accounted for by the general splanchnomegaly of the disease. Hence it is natural to assume that the thyroid must be responsible for the accelerated tissue combustion, and there are certain facts which may be interpreted as lending support to this view, even though enforced recum-

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<sup>10</sup> Boothby, W. M., and Sandiford, I. Summary of the Basal Metabolism data on 8,614 Subjects, with Special Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *J. Biol. Chem.* **54** 783 (Dec.) 1922.

bency does not appear to influence the elevated metabolism in acromegaly so favorably as it does in hyperthyroidism

In an earlier article in this series <sup>11</sup> it was pointed out that a palpable or definitely enlarged thyroid was recorded in twenty-five of the hundred patients with acromegaly. Of these twenty-five cases, seventeen happened to have reliable determinations of their metabolism, fifteen of them showing an elevated rate. To give the exact figures

In forty-nine cases with a B M R of +3 per cent to +61 per cent, an enlargement of the thyroid was present in fifteen (30.6 per cent), three of the patients having had a thyroidectomy, with recurrence of the goiter in two of the three. On the other hand, in twenty-three cases with a B M R of -2 to -17 per cent, only two (8.7 per cent) had palpably enlarged thyroids. Excluding the thirty-two cases with a rate between -10 per cent and +10 per cent as falling within the possible limits of normal, there remain seven cases with a rate below -10 per cent, and thirty-three with a rate above +10 per cent. Eight of the latter group had enlarged thyroids, whereas in none of those with definitely lowered metabolism was the gland appreciably enlarged.

The inference might therefore be drawn that an elevated metabolic rate in acromegaly and an enlargement of the thyroid go hand in hand, which is far from true, for in 75 per cent of the cases with definitely elevated metabolism the thyroid was not even palpable. We consequently must look for evidence from other sources, and it would seem at first sight that the problem involved should present no great difficulties of solution. As a matter of fact, it does, and a final answer may not be forthcoming until an active anterior-lobe principle is isolated, so that we can determine its independent effect on body metabolism and compare it with the reactions of thyroxin. However, while awaiting that time, light may be thrown on the subject by certain contributory observations. For if the thyroid is responsible, the excised gland should show the characteristic histologic changes of the exophthalmic or adenomatous goiter, and the metabolic rate should be definitely lowered by the procedure. If the acromegalic adenoma, on the other hand, is responsible, its excision or treatment by radiation should serve to lower the rate, and if it does so in the absence of goiter, the hypophysis may be considered to influence the metabolism independently of the thyroid.

#### THE QUESTION PRIMARILY FROM THE STANDPOINT OF THE THYROID

The thyroid as is well known is often enlarged in acromegaly, sometimes greatly so. When removed, as it may have to be because of dyspnea from tracheal compression,<sup>12</sup> if for no other reason, it has

11 Davidoff, L. M. Studies in Acromegaly. III. Anamnesis and Symptomatology of One Hundred Cases, *Endocrinology* **10** 461, 1926

12 Cushing, H. The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Co. 1912, p. 150, case 29

usually proved to be a colloid goiter. Moreover, the gland as found and described at autopsy in cases of acromegaly has invariably been of the colloid type and free from those microscopic changes which are seen in hyperthyroidism. This would seem at first sight to speak strongly against the view that the increased metabolism so often met with in the disease is thyrogenic. But so far as we are aware, there is no recorded autopsy report in which recent ante mortem determinations for metabolism had been taken. It would be impossible to deny, therefore, that all these patients with colloid goiter were not by chance observed when the thyroid happened to be in an inactive or resting stage.

(a) *Thyroidectomy for the Goiter of Acromegaly*—For more exact information one must therefore turn to surgery. However, though operations for hyperthyroidism are common, and though in most modern clinics the respiration apparatus is in general use, it is unusual for thyroidectomies to be performed on unquestioned cases of acromegaly, nor are these operations likely to be performed on patients in whom dependable preliminary estimations of the metabolic rate have shown that this rate is not definitely increased.<sup>13</sup> Fortunately for our purposes, we have had three such cases under observation. They are as follows:

CASE 1—*Outspoken acromegaly in a middle-aged woman with large goiter and supposed hyperthyroidism in view of high B M R. Thyroidectomy, colloid goiter, lowering of B M R*

Mrs. E. E. R., aged 47, referred by Dr. Horace Johnson of Brownville, Me., was admitted to the hospital on Feb. 26, 1917, with the following complaints: enlargement of the bones of the hands, feet and skull, goiter, dyspnea and nervousness.

Her childhood was without especial ill health. Catamenia appeared at 16. She was married at 28, and subsequently had four miscarriages all during the third month of pregnancy. Regular menstruation continued till she was 45, when the menopause set in.

Her present illness dated from the age of 30, when she acquired a goiter which had not given her special trouble and had remained stationary in size for the past five years. Since she was young, there had been occasional attacks of cardiac palpitation with vomiting. Not long after the first appearance of the goiter, her hands and feet began to enlarge, and she had to increase the size of her gloves and shoes every few months. At the same time there was a great change in her features, accompanied by marked prognathism; there also was a definite increase in stature. Coincident with these changes in growth she gained nearly 40 pounds (18.1 Kg.) in weight (from 128 to 165 pounds) and experienced great fatigability, weakness and numbness of the extremities. Recently she had observed impairment of vision. At one time, a few months

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13 The literature on the subject is meager. A few cases of hyperthyroidism in patients with acromegaly have been recorded but without B M R determinations or operative verification (Claude, H. *Syndrome d'hyperfonctionnement des glandes sanguines chez des acromegaliques*, Soc. de Biol. **59** 362, 1905). Far more frequently a condition spoken of as myxedema has been described in cases of acromegaly with goiter (Modena, G. *L'acromegalia Riv. Sper. di Freniat.* **29** 629, 1903).

before admission, there appeared to have been a period of subjectively observed hemianopia. She had no special complaint of headaches.

Sixteen months before admission she was deserted by her husband and had since been obliged to support herself. To this she ascribed her present dyspnea, for which she chiefly had entered the hospital. She had lost over 20 pounds (9.0 Kg.) in weight in the meantime.



Fig 1 (case 1)—Patient with acromegaly, goiter, and elevated basal metabolic rate

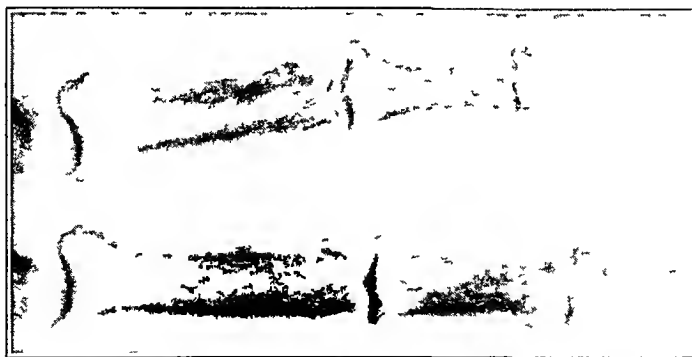


Fig 2 (case 1)—Index and middle fingers to show telltale acromegalic phalangeal tufting with hyperostoses

The physical examination showed a middle-aged woman (fig 1) with typically acromegalic features, extremities and kyphosis. The roentgen ray showed the characteristic terminal phalangeal tufts (fig 2) with hyperostoses of the bones elsewhere, also a greatly hypertrophied cranial vault about 2 cm

in thickness, with mandibular prognathism. The sella was enlarged, measuring 30 mm in an anteroposterior diameter and 25 mm in depth (fig 3). There were, however, no changes in the eyegrounds and no perimetric field defects. The heart was enlarged but compensation was good. The skin was bathed in sweat and considerably pigmented. Blood tests and urinalysis were negative.

*The Goiter*—The gland was large and full but with no thrill or bruit. The pulse varied around 80, but occasionally rose to 120. The temperature tended to be slightly subnormal. The blood pressure showed some hypertension: systolic, 190, diastolic, 130. There were none of the eye signs of exophthalmic goiter, no tremor. Her B M R on March 5 was +61 per cent.

Here was a woman with unmistakable acromegaly and a large goiter compressing the trachea, as was shown by the roentgen ray. This appar-

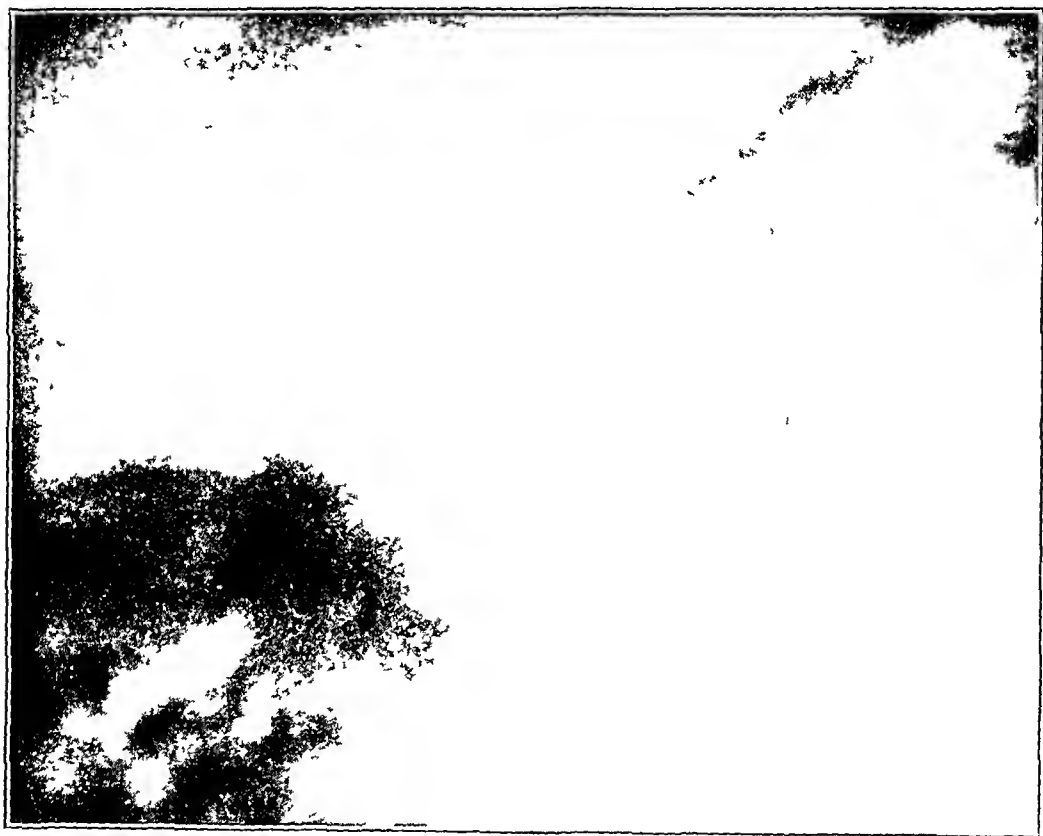


Fig 3 (case 1) —Greatly enlarged sella (natural size)

ently was the cause of her dyspnea. A recent accession of symptoms with nervousness and loss of weight even in the absence of marked tachycardia suggested a wave of hyperthyroidism which the unusually high metabolic rate served to substantiate. An operation was consequently decided on.

On May 5, 1917, Dr. Homans ligated the right superior thyroid artery. There was considerable reaction which subsided in a few days. On May 11, the B M R was +49 per cent.

On May 14 the left superior thyroid was ligated. Again there was considerable reaction which subsided. On May 19, the B M R was +52 per cent. On June 6, it had fallen to +46 per cent, on June 25, it was +48 per cent.

On June 27, Dr Cheever performed a subtotal thyroidectomy under local anesthesia. The trachea was found considerably flattened. The gland (fig 4) proved to be of the adenomatous colloid type, and although the epithelium was cuboidal, areas suggesting toxicity were not found. The patient made a rather poor convalescence with rapid pulse and fever for the first three days and a definite increase in her nervousness. On July 2, her B M R was +62 per cent, on July 10, it had fallen to +31 per cent. She was discharged on July 13, her dyspnea was improved, but her symptoms were not greatly altered otherwise.

She was not heard from again until July 10, 1925, eight years later, when in reply to a letter of inquiry it was stated that, "Her general health seems very good, but she has occasional cardiac attacks with difficult breathing. She continues to have a very large appetite and is strong, but sleeps half the time. She will often be asleep ten minutes after her breakfast."

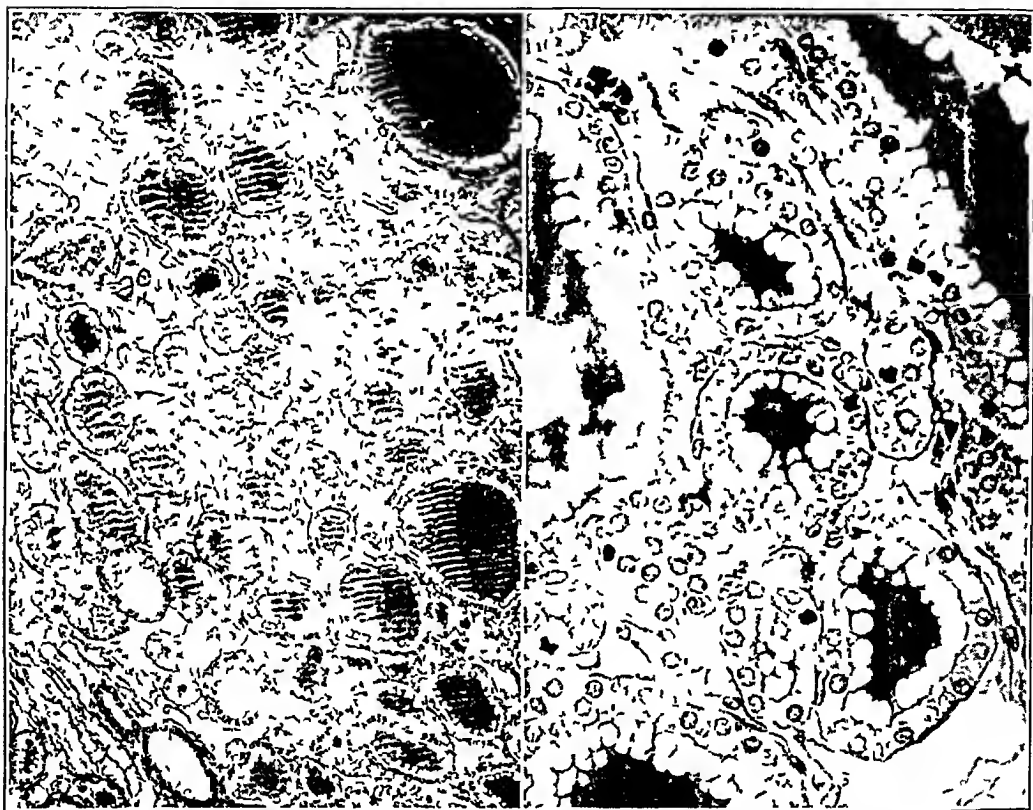


Fig 4 (case 1) —Adenomatous thyroid. Hematoxylin and eosin stain,  $\times 80$  (left),  $\times 300$  (right).

Since a goiter of the type removed in this case is not usually associated with a marked increase in metabolism, one naturally must look for some other agency to explain the elevated metabolism. On the other hand, the elevated rate was reduced fully one half by the thyroidectomy. Whether one is to believe that the patient had a toxic goiter, histologic evidence of which is lacking in the opinion of several experienced observers, or that her high rate of metabolism was of pituitary origin and was lowered by the removal of a secondarily activated goiter, is a matter that might be argued. The history of the second case follows.

*CASE 2—Incipient acromegaly with increased metabolism, operated on for coincidental goiter. Subsequent drop in the B M R. Advancing acromegaly with increase in the rate and a spontaneous drop to normal*

Mrs E F, Swedish, aged 34, referred by Dr Howard M Clute of the Lahey Clinic, was admitted to the hospital on Oct 8, 1925, with the complaint of acromegaly and its complications. She had had a small goiter since childhood. Her mother and sister also had goiter.

Enlargement of the extremities and features, with excessive sweating and hypertrichosis, had been apparent for possibly nine years. Headaches had lately become pronounced. Irregular menstruation for two or three years had been followed during the nine months previous to admission to the Brigham Hospital by total amenorrhea.

On Jan 11, 1923, she had gone to the Lahey Clinic complaining of her goiter which recently had been rapidly increasing in size, and which had given



Fig 5 (case 2)—Acromegalic woman after recent thyroidectomy for presumed hyperthyroidism

her a sense of dyspnea on raising her arms. Associated with this she complained of nervousness, irritability, sweating and some pains in the arms and hands.

These symptoms were naturally ascribed to mild hyperthyroidism, and the view was supported when on January 24 the metabolic rate was +24 per cent. There were no eye signs, no diarrhea nor tremor. The pulse had varied from 80 to 94. The menses were recorded as regular. The weight was 135 pounds (61.2 Kg).

On January 25, a subtotal thyroidectomy was performed by Dr Lahey for "a multiple colloid adenomatous goiter with secondary hyperthyroidism." The patient made an excellent operative recovery. On Feb 2, 1923, the B M R was +13 per cent, weight was 122 pounds (53.3 Kg). On June 20, the metabolism had fallen to +2 per cent, and on August 25 to -3 per cent, with

an increase of weight to 131 pounds (59.4 Kg). Her general condition remained unaltered. The goiter began to grow again, and she had been given Lugol's solution without effect. Her complaint of headache increased, it was suspected that she might have acromegaly, and in October, 1925, she was referred to the Brigham Hospital.

By this time the diagnosis was unmistakable (fig 5), the sella was slightly enlarged (fig 6), and the terminal phalangeal tufting was pronounced (fig 7). On October 9, 1925, the B M R was  $+28$  per cent, the weight was 134.2 pounds (60.8 Kg). Visual field defects were not demonstrable, and she was discharged without treatment.

On November 23, her B M R was  $+3$  per cent, and again on December 12, it was  $+6$  per cent. After this she was given a series of deep therapeutic



Fig 6 (case 2) —Slightly enlarged sella

radiations to the hypophysis. This was followed by subjective improvement in her headaches and in the numbness and tingling in her extremities.

On June 24, 1926, she was readmitted for study. Her general subjective improvement had continued. There appeared to be no increase in her acromegaly. Her B M R was  $+2$  per cent, her weight was 134.8 pounds (61.0 Kg).

Here, then, was another case of acromegaly with increased metabolism and an associated goiter which at operation proved to be of the colloid type. Doubtless the early acromegalic symptoms were obscured by the symptoms suggesting mild hyperthyroidism. Her metabolism of  $+27$  per cent dropped to approximately normal in the course of five

months after a subtotal thyroidectomy Two years later, with increasing acromegalism and regrowth of her goiter, she had a metabolism of  $+28$  per cent, somewhat higher than before the thyroidectomy This increased rate spontaneously subsided and has remained low The accuracy of the observations can hardly be questioned The interpretation is difficult The third of these three cases follows

*CASE 3—Rapidly advancing acromegaly in a young woman with slightly increased B M R A subtotal thyroidectomy for a supposed toxic goiter which proved to be of the colloid type B M R reduced*

Miss B M, aged 26, a stenographer, referred by Dr W A Sullivan of Nashville, Tenn, was admitted to the hospital on Aug 17, 1925, because of her rapidly advancing hyperpituitarism associated with a choked disk Her outstanding complaint was of intolerable headache and discomfort in her throat

*Anamnesis*—Since childhood she had suffered from periodic "sick headache" About six years ago, when she was about 19 years of age, she began to have cephalalgia of another kind—pains in the head extending into the back and shoulders and associated with a gripping pain in the throat

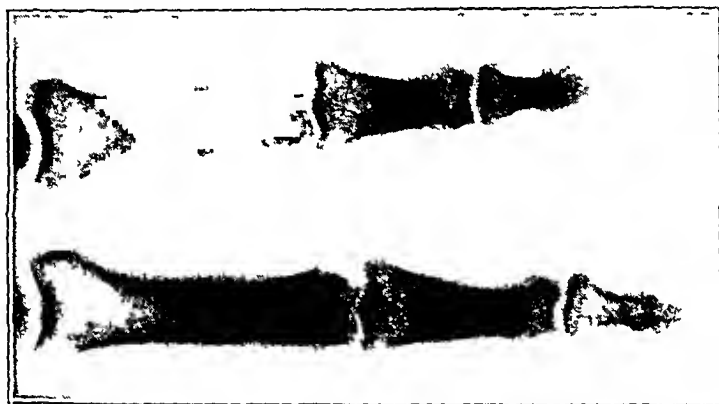


Fig 7 (case 2)—Moderate terminal phalangeal tufting, a telltale of acromegaly

It was not until 1921, two years later, that a marked enlargement of her extremities became noticeable Coincidentally, the change in her features was so great that she became unrecognizable to persons who had previously known her From the beginning of the condition she had had a ravenous appetite, and there had been a progressive gain in weight 116 pounds (52.6 Kg) in 1919, 132 pounds (59.9 Kg) in 1921, 140 pounds (63.5 Kg) on admission

Her menses began at the age of 12, continued to be regular until about eighteen months ago, and since August, 1924, amenorrhea had been complete She had suffered all this time from marked hyperhidrosis and during the later stages of the disease from furunculosis

She had undergone a variety of minor operations in the course of her malady Most of her teeth, which had become widely spaced, had been extracted Her tonsils and adenoids had been removed

On April 9, 1924, a subtotal thyroidectomy had been performed by Dr A H Kegel of Chicago, to whom we are indebted for the surgical history She was supposed to have a toxic goiter in view of the symmetrically enlarged and pulsating gland associated with an elevated B M R showing on three separate sessions  $+35$ ,  $+35$  and  $+42$  per cent

The thyroid on removal proved to be merely a colloid goiter No subjective improvement in the patient's condition followed the operation Seven months

later she had been referred to the Mayo Clinic, where, in November, 1924, the B M R was +15 per cent. Her hypophysis had meanwhile been subjected to therapeutic radiations.

The physical examination on admission to the Brigham Hospital showed a young woman with hypertrophied extremities and features, puffy tissues, hypertrichosis of masculine type, hyperhidrosis, prognathism and the hyper-



Fig 8 (case 3) —A young woman with *acromegalia fruste* after a thyroidec-tomy for supposed primary hyperthyroidism

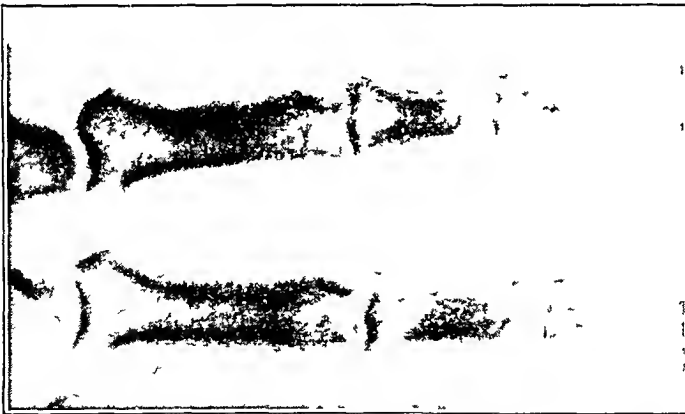


Fig 9 (case 3) —Moderate tufting of terminal phalanges

trophied tongue characteristic of outspoken acromegaly (fig 8). The roent-gen rays revealed the bony changes typical of the disease (fig 9), but with a sella only moderately enlarged (fig 10).

There was a left temporal hemianopia to colors, but instead of the usual pallor the disks showed a slight papilledema. She had also a relative anosmia, only strong odors being perceived. The heart was slightly enlarged. There was evidence of some hypertension: systolic pressure, 170, diastolic, 130. The urine was normal, without sugar or albumin. Her B M R was +5 per cent.

In view of the comparatively small sella and the distressing headaches accompanied by low grade of papilledema, an intracranial extension of her adenoma was suspected. She was given a roentgen-ray treatment and discharged. She did badly and reentered the hospital on Feb 27, 1926. The evidences of overgrowth had definitely advanced. The clinical symptoms at the time were dominated by the signs of intracranial pressure. She had a high grade of choked disk which had progressed to blindness in the left eye and near blindness in the right. Her B M R was +10 per cent. A subtemporal decompression was performed disclosing a tense brain. The operation gave practically no relief.

The last report, received Sept 24, 1926, was that her condition was becoming worse.



Fig 10 (case 3) —Moderately enlarged sella of acromegaly

Here again was a woman with a rapidly advancing acromegaly in whom a toxic adenoma was suspected because of her goiter and elevated metabolism. The goiter again proved to be of the colloid adenomatous type. Although her subjective symptoms were not improved, her B M R after a period of seven months had fallen approximately to high normal levels, and a year later, possibly under the influence of hypophyseal radiotherapy, the rate had dropped another 10 points. Meanwhile the hypophyseal adenoma had evidently extended widely into the intracranial chamber.

Considering these three cases together, even though in all of them the B M R was appreciably lower after the operations, one may conclude that in the absence of sufficient microscopic evidences of thyroid overactivity to account for the elevated metabolism which the patients

showed at the time of operation, this must be ascribed to some cause other than to hyperthyroidism alone<sup>14</sup>

(b) *The Effect of Lugol's Solution*—Mention was made, in the notes on the second case, of Lugol's solution having been employed without the expected effect, this, with one notable exception, has been our experience in the few cases under our personal observation in which it has been administered to patients with acromegaly with increased metabolism and enlarged thyroid glands. In one patient, for example, with a metabolic rate of +26 per cent, 5 drops of Lugol's solution three times a day was administered over a period of fourteen days, and the B M R rate estimated every forty-eight hours, without the slightest effect being shown, whereas ten days after a hypophysectomy it had dropped to zero and remained there. The exception was a recent observation, which proves to be a most striking one.

CASE 4—The patient, Miss E. A. C., a school teacher, aged 35, first came under observation on Nov. 15, 1913. She was a cooperative and intelligent woman with marked acromegalic changes of four years' duration. Eight months later (July 16, 1914), owing to increasing headaches, asthenia and beginning bitemporal constriction of her fields of vision, she was readmitted to the hospital and a transphenoidal operation was performed. A tense gland was encountered, and a fairly radical intracapsular removal of adenomatous tissue (chromophile) was carried out.

She made an excellent recovery, with marked subjective improvement in headaches, vision and size of the extremities. This improvement lasted for nearly eight years, although there was in the interval an obvious increase in her acromegalic appearance.

In the summer of 1921 she began to notice a definite thyroid enlargement associated with "nervousness," the symptoms improving under iodine. During the next four or five years the thyroid progressively enlarged, and although she continued to be nervous and to show periodic waves of glycosuria, she managed to continue her teaching.

She came under observation again in November, 1925, with a mild diabetes. Her basal metabolism was then taken for the first time, the rate averaging +41 per cent and +39 per cent on two different occasions. She, however, did not have marked tachycardia, the pulse rate being about 90, her temperature tended to be subnormal and there was some doubt of her actually having thyreotoxicosis.

She recently returned for the purpose of submitting to a test with Lugol's fluid. The thyroid was even more enlarged, her metabolism was still high and she complained of nervousness and sleeplessness. There was, however, no tachycardia, the pulse averaging 80, her temperature was normal, and she was in a period of freedom from glycosuria. The complete list of her metabolism determination may be here assembled, and it should be pointed out that between July 8 and August 13 she had been resting and taking heliotherapy under most favorable circumstances.

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14 In a personal communication, Dr. Irene Sandiford of the Mayo Clinic writes, on Aug. 17, 1926, that thyroidectomy has been performed there on fourteen patients with acromegaly, thirteen times for toxic adenoma and once for exophthalmic goiter, that in only nine of the cases were rates taken both before and after the operation, that of these nine, five showed increased or only slightly decreased postoperative rates, and four showed normal rates.

Nov 26, 1925	+ 41
Nov 30, 1925	+ 39
July 8, 1926	+ 37
Aug 13, 1926	+ 34

Lugol's solution begun, 5 drops, three times a day

Aug 16, 1926	+ 29
Aug 18, 1926	+ 21
Aug 20, 1926	+ 18
Aug 23, 1926	+ 21
Aug 25, 1926	+ 23
Aug 27, 1926	+ 12
Aug 31, 1926	+ 10

Lugol's solution discontinued

Sept 2, 1926	+ 6
Sept 4, 1926	— 1

This extraordinary and progressive drop in the metabolism under the administration of Lugol's solution was almost more than one would expect in exophthalmic goiter, and in the experience of this hospital the metabolism of the patient with ordinary toxic adenomatous goiter is unaffected by Lugol's solution. The patient meanwhile experienced marked subjective improvement. She slept more soundly than usual, was free from nervousness, and the large goiter became perceptibly smaller, hard and nodular. Certainly the response was as definite as one ever sees in thyrotoxicosis. The patient, unfortunately, had to leave for her school before we could learn whether there was to be a reelevation of the rate, which continued to drop for four days after the Lugol's solution was discontinued.

We may therefore conclude that Lugol's solution is capable in certain cases of lowering the increased metabolic rate of acromegaly in a striking way, and might naturally assume that it does so by an effect on the thyroid.

To this point the testimony would seem to be largely in favor of the thyroid, it being assumed that the colloid goiters, which have been observed, merely represent the end stages or temporary resting periods of waves of hyperthyroidism, this, according to Marine's view, being the way in which a colloid goiter is formed. The tissues in the first case, though pronounced a colloid thyroid (fig 4), have a definitely active look even though the picture does not bear resemblance to that of a toxic goiter. How quickly the picture of exophthalmic goiter may change under the effects of iodine to that of a colloid goiter has recently been well shown by Rienhoff<sup>15</sup>

It must not be forgotten that a number of cases of exophthalmic goiter have been described as coexistent with acromegaly. The perusal of the case histories, however, leaves one somewhat in doubt as to the dependableness of the diagnoses, the cases being no more convincing

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<sup>15</sup> Rienhoff, W. F. Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter and Their Relation to the Origin of Certain of the So-Called Adenomas, *Arch Surg* **13** 391 (Sept) 1926

than the three herein reported, and the puffiness of the eyelids with protrusion of the eyeballs from increase in intra-orbital tissues often seen in acromegaly, might easily mislead the unwary. But, all told, there is nothing in the evidence so far that would contradict the possibility that primary hyperthyroidism and primary hyperpituitarism may coexist in the same patient.

#### THE QUESTION FROM THE STANDPOINT PRIMARILY OF THE HYPOPHYSIS

On the principle that removal of the goiter, or its direct treatment by radiation in cases of hyperthyroidism causes a symptomatic improvement, of which the lowering of the basal metabolic rate proves to be a more or less satisfactory measure, one might assume that corresponding procedures on the hypophysis in cases of hyperpituitarism with increased metabolism ought to show comparable effects. Although for a number of reasons the observations on which the test of this assumption must rest are few, they appear to be fairly conclusive.

(a) *The Effect of Radiation*—It has been unusual for patients in the series to be subjected to hypophysial radiation alone, nor have those so treated often appeared to be greatly benefited thereby. Unusually there have been definite indications necessitating operative intervention, and several of these patients have been treated by a combination of surgical measures and subsequent radiation. An occasional patient, however, has been given roentgen-ray treatment alone and has shown a subsequent fall in metabolism with definite improvement in symptoms. The following is an example.

CASE 5—*Outspoken acromegaly in an adult male, treated by deep hypophysial radiation. Subsequent fall in B M R*

C H W, a huge acromegalic man, aged 46, first entered the hospital on July 13, 1925, complaining of his disfigured appearance, somnolence, irritability, poor memory, pain and tingling in the feet, fainting spells and excessive perspiration. His sella turcica was moderately enlarged, but his visual acuity, optic disks and fields of vision showed no variations from normal. The B M R was +40 per cent. The thyroid was not palpable.

In the absence of any pressure symptoms, he was given a series of deep roentgen-ray radiations. Treatments were begun here on July 17, 1925, and continued with approximately three week intervals, under adequate supervision, in another city until six treatments had been given. On September 8, his metabolic rate had dropped to +29 per cent, and October 1 to -10 per cent. Meanwhile he experienced definite improvement in his symptoms.

In the course of two months after his last radiation his condition had definitely retrogressed, and he was readmitted to the Brigham Hospital, where on January 15, 1926, his B M R was again found to be +45 per cent. Another series of roentgen-ray treatments was begun, and these were again followed by definite subjective improvement. By June 30, 1926, the rate had dropped to +24 per cent, and on October 13, when he reported here to have his condition checked up, it was found to be +10 per cent. He has not been so free from his distressing symptoms of "acromegalism" for years.

(b) *The Effect of Operation*—Far more significant and striking are the results of the surgical procedures. Formerly, operations for pituitary tumors were carried out with the single object of relieving the optic chiasm from pressure and saving vision. In this sense they were comparable to the early operations for goiter which were conducted solely for the relief of dyspnea due to compression of the trachea. In each instance the disturbances were mechanical, and mechanical procedures were needed to relieve them.

Operations on the thyroid, however, have long since passed beyond this early and restricted use, and are now largely employed to counteract the toxic effects of hyperthyroidism, which does not necessarily imply a large tumor. Just so we may expect hypophyseal operations, although technically far more difficult, to be employed more and more often in acromegaly to counteract the effects of the hyperpituitarism irrespective of the size and pressure effects of the adenoma.

In either case, the size of the tumor is no measure of the activity or severity of the disease. What concerns us far more than size is the relative amount of tissue removed, for a mere decompression of the sella to relieve pressure symptoms in a case of acromegaly should have no effect in changing the metabolic rate. With the improvement in the technic of these operations in recent years, the extirpation has become increasingly radical, and the effects in modifying the symptoms are becoming more lasting, more definite and more nearly comparable to the effects of a subtotal thyroidectomy.

Even though the number of hypophysectomies for uncomplicated acromegaly on which reliance may be placed is few, they are sufficiently definite for our present purposes. As it happens, dependable metabolism determinations were made in only thirty-nine of the fifty-six acromegalic patients in the series subjected to operation and in only eighteen of these thirty-nine cases are both preoperative and postoperative observations recorded. Before operation the eighteen cases showed a B M R ranging from  $-14$  per cent to  $+32$  per cent (average  $+10$  per cent), after operation they ranged from  $-19$  per cent to  $+13$  per cent (average  $-7$  per cent), showing a total average drop per case of 17 per cent.

This disclosure that not only the patients with originally high determinations but also those with a low or even subnormal preoperative B M R showed on the average a significant lowering of the rate subsequent to operation, suggests that the operation per se might be responsible, particularly since in several of these cases the amount of adenomatous tissue removed was not particularly great. The postoperative determinations were deferred until the patient had fully recovered from the immediate effects of the operation and was up and about the ward. But there are sufficient reasons to discard this possible

explanation of the postoperative fall in rate, for such comparable changes in the rate are not seen in the patients operated on for pituitary adenomas with hypopituitarism. These operations are more common and the extirpation more likely to be radical, and yet the metabolism determinations are likely to remain, on the average, approximately at their former level.

In a series of twenty-four patients with hypopituitarism associated with surgically verified chromophobe adenomas, in whom metabolism studies were made both before and after operation, the results were as follows. Before operation the twenty-four patients showed a metabolic rate ranging from  $-32$  per cent to  $-3$  per cent (average  $-16.1$  per cent), after operation they ranged from  $-39$  per cent to  $-5$  per cent (average  $-17.7$  per cent), showing a total average drop of only  $1.6$  per cent. The contrast between these patients and those with acromegaly may be seen at a glance in table 1.

TABLE 1—*The Basal Metabolic Rate of Patients with Acromegaly and That of Patients with Hypopituitarism*

	Number of Cases	Average Basal Metabolic Rate		Average Drop in Metabolic Rate
		Before Operation	After Operation	
Acromegaly	17	+10.0%	-7.0%	17.0%
Hypopituitarism	21	-16.1%	-17.7%	1.6%

In addition to the fall in metabolism, the acromegalic patients are likely to have a distinct and early change in appearance so far as the malady affects the soft parts. This is shown by a definite improvement in the texture of the skin, a distinct reduction in the size of the hands and feet, often first noticed by the patient himself. That the change is not born of the patient's expectancy is shown by actual change in measurements, to be accounted for by the disappearance or lessening of the peculiar acromegalic "myxedema." Associated with this improvement in the extremities there is often a considerable loss of weight, not infrequently 10 or 12 pounds (4.5 or 5.4 Kg.), this can hardly be ascribed to the operation itself, which is remarkably well borne by these patients, and a corresponding loss of weight does not occur after similar operations on patients with hypopituitarism.

It would appear, therefore, that the further lowering of even a subnormal metabolism in the series of patients with acromegaly may have some significance, and that our formula for calculating the rate in these patients may place the normal too high.<sup>16</sup> However this may be, the cases in which a definitely elevated rate of  $+10$  per cent or more was

16 The Harris-Benedict standard in general gives values 5 per cent lower than the DuBois standard, and Dr. Benedict has recently suggested that the standard for women should be 5 per cent lower than this.

lowered by the operation are sufficiently striking to bear alone the brunt of the argument. There are nine cases that fall in this group, the changes in rate which had taken place in about two to three weeks after operation being shown in table 2.

These were all outspoken examples of acromegaly. Only one of the patients had a palpably enlarged thyroid. Another had a condition of complicating diabetes which, however, should not have modified the metabolic rate. The majority of them had large pituitary adenomas giving local pressure symptoms, although in one of them the gland was only slightly enlarged and in another scarcely enlarged at all (case 7). Brief abstracts of the histories are given below.

CASE 1—Mrs. H., a Hungarian woman, aged 24, was admitted to the hospital on March 15, 1916. She had been married at 19 and a year later had given birth to a normal child. Following this pregnancy, her menses were never restored. She soon began to have severe headaches and photophobia with marked weakness and drowsiness, numbness of the extremities and excessive sweating, accompanied by enlargement of the extremities and features.

TABLE 2—*Changes in the Basal Metabolic Rate Before and After Operation*

Case	Complications	Before Operation	After Operation
1	Goiter	+18	+2
2		+15	+3
3		+21	+6
4		+31	+13
5		+32	+12
6	Diabetes Glycosuria	+38	+13
7		+25	0
8		+24	+4
9		+16	+3

Examination showed a typical acromegalic patient with an enlarged thyroid, but tremor, tachycardia, exophthalmos or other evidences of hyperthyroidism were not present. The sella was much enlarged (21 mm by 17 mm), and although there was some pallor of the disks, the visual fields were normal.

On March 17, her height was 158 cm (5 ft 3 in), her weight 158.4 pounds (71.8 Kg), the pulse rate was 88, the temperature 98.6, and the B. M. R. +18 per cent.

On March 24, a transphenoidal operation was performed in the hope of relieving her severe headaches even though evidence of chiasmal pressure was lacking. The dura was under great tension, and on opening it tense (chromophile) adenoma began to extrude and a considerable amount of it, for the time (1916) was removed. The patient made an excellent recovery, with complete relief from headaches.

On April 5, her weight was 147 pounds (66.7 Kg), temperature, 98.7 F, pulse rate 69 and B. M. R. +2 per cent.

Here, then, was a patient with an enlarged thyroid and slightly increased metabolism whose metabolic rate dropped 16 per cent subsequent to an uncomplicated operation on the hypophysis with partial removal of an adenoma. The following cases all represent similar procedures with corresponding results on patients without palpable enlargement of the thyroid.

CASE 2—Mrs B F, aged 23, was admitted to the hospital on Feb 20, 1914. Symptoms of acromegaly were first noticed three years previously during her first and only pregnancy. A healthy child was born, which was breast fed. Normal catamenia never became reestablished. In addition to the acral overgrowth, there were polyphagia, headaches, darkening of the skin, increased hirsutes, deepening of the voice, and other symptoms.

Examination showed a moderately enlarged sella but no eye changes. Determinations for metabolism were not made.

In December, 1914, she again came under observation. Her symptoms were definitely increased, and there were beginning bitemporal field defects and a further enlargement of the sella.

On Oct 21, 1915, she reentered the hospital for operation owing to a still further advance in symptoms. From the time of her first admission she had gained 35 pounds (15.9 Kg).

On October 27, her height was 171.5 cm (5 ft 8½ in), weight 190.8 pounds (86.4 Kg), temperature, 98.4 F, pulse rate 88 and B M R +15 per cent.

On October 27, a transphenoidal operation was performed with sellar decompression and fragmentary removal of an adenoma, which was shown to be chromophilic. Convalescence was uneventful.

On November 9, her weight was 182 pounds (82.6 Kg), temperature 98.8 F, pulse rate 80, and B M R +3 per cent.

CASE 3—Mrs J A L, aged 33, was admitted to the hospital on Jan 8, 1917, with a history of obvious acromegaly of about eight years' duration. Onset with headaches, enlargement of extremities, numbness and tingling, asthenia, drowsiness, nervousness, increase in weight from 142 to 170 pounds (64.4 to 77.1 Kg), irregular menstruation, increase in hirsutes, and other symptoms.

Examination showed advanced acromegalic changes with a moderately enlarged sella and early bitemporal field defects. The thyroid was palpable. She had enormously enlarged tonsils which were giving her trouble, and these were removed. She reentered the hospital three months later.

On April 4, 1917, her height was 157 cm (5 ft 2½ in), weight 149.8 pounds (67.8 Kg), temperature 97.8 F, pulse rate 80, and B M R +21 per cent.

On April 9, a transphenoidal operation was performed with extirpation of a considerable amount of adenomatous tissue which proved to be acidophilic. Convalescence was uneventful, there was marked improvement in appearance.

On April 23, her weight was 143.8 pounds (65.1 Kg), temperature 98.6 F, pulse rate 72, and B M R +6 per cent.

She was not seen again until two years later. She was greatly improved, although she still experienced occasional exacerbations of her previous symptoms. Curiously enough, normal menstruation had become reestablished. The B M R was not taken.

CASE 4—Joseph S, a machinist, aged 20, admitted to the hospital on March 24, 1924, had rapidly advancing acromegaly of only seven months' duration. His symptoms were rapid increase in the size of the extremities and face, a period of marked glycosuria, blurring of vision, drowsiness, apathy, increase in weight and impotence.

Examination showed in addition to the marked overgrowth a large sella, optic atrophy and bitemporal hemianopia.

On March 25, his height was 174.5 cm (5 ft 9¾ in), weight 156.2 pounds (70.9 Kg), temperature 98.5 F, pulse rate 83, and B M R +31 per cent.

On April 5, a transphenoidal operation was performed with fairly extensive removal of adenomatous (acidophilic) tissue. Convalescence was uneventful. A postoperative B M R estimation was not made. The patient was given a series of roentgen-ray treatments and temporarily passed from observation with a marked change for the better in his appearance.

On Feb 26, 1925, his weight was 147 pounds (66.7 Kg), temperature 98.6 F, pulse rate 74, and B M R +13 per cent.

CASE 5—Mrs F P, aged 48, was admitted to the hospital on April 19, 1925, with a history dating back fourteen years when, in association with headaches and photophobia, acromegalic changes became pronounced. Subsequently amenorrhea, lethargy, disturbance of vision, excessive sweating, increase of weight, loss of strength, polyphagia and other symptoms appeared. Examination showed a large sella, optic atrophy and blindness in the right eye with left temporal hemianopia. There was no glycosuria, and the thyroid was not palpable.

On April 22, her height was 165.6 cm (5 ft, 6 in), weight 179.7 pounds (81.4 Kg), temperature 98.4 F, pulse rate 84, and B M R +32 per cent.

On April 28, a transphenoidal operation was performed with extensive removal of adenomatous tissue found to be eosinophilic. Convalescence was uncomplicated, and there was definite improvement in symptoms.

On May 14, her weight was 173.1 pounds (78.5 Kg), temperature 98 F, pulse rate 98, and B M R +23 per cent.

On May 20, her weight was 175.1 pounds (79.4 Kg), temperature 98 F, pulse rate 84, and B M R +12 per cent.

CASE 6—R H, a farmer, aged 41, was admitted to the hospital on Nov 25, 1925, with a history of progressive acromegaly over a period of nineteen years. A condition of complicating diabetes had been observed for six years. Examination showed a full-blown example of the disease with large sella, optic atrophy, and one eye completely blind. The thyroid was not palpable.

On November 27, his height was 172.8 cm (5 ft, 9.1 in), weight 159.7 pounds (72.3 Kg), temperature 97.2 F, pulse rate 81 and B M R +38 per cent. His B M R was studied on various occasions before and after the administration of insulin and before and after the administration of Lugol's solution, neither had any appreciable effect.

On December 23, a transphenoidal operation was performed with extensive removal by suction of soft adenomatous tissue which proved to be acidophilic. There was an uncomplicated convalescence with subjective improvement.

On Jan 1, 1926, his weight was 157 pounds (71.2 Kg), temperature 98.2 F, pulse rate 96, and B M R +30 per cent.

January 27, his weight was 164.7 pounds (74.6 Kg), temperature 97 F, pulse rate 80, and B M R +13 per cent.

CASE 7—Mrs Lucia S, an Italian woman, aged 22, was admitted to the hospital on Dec 17, 1925. Two years before, during a pregnancy, there had been an onset of her present illness with severe headaches, marked increase in weight and enlargement of the extremities. The menses were normal. The thyroid was barely palpable, the sella was scarcely enlarged, and there were no eye signs, the pulse rate was from 80 to 90.

The patient was readmitted on Aug 27, 1926, with a history of continued severe headaches.

On August 30, her height was 157 cm (5 ft, 2 in), weight 204 pounds (92.5 Kg), temperature 98.4, pulse rate 84, and B M R +25 per cent. The B M R, which was repeated in two days, was +24 per cent.

On September 2, the administering of Lugol's solution, 5 drops three times a day, was started and continued for fourteen days—until September 16.

On September 4, the B M R was +19 per cent.

On September 7, the B M R was +26 per cent.

On September 9, the B M R was +25 per cent.

On September 11, the B M R was +20 per cent.

On September 14, the B M R was +16 per cent.

On September 16, the B M R was +21 per cent.

On September 20, a transphenoidal operation, with radical hypophysectomy, was performed. There was immediate relief of headache and prompt and uneventful recovery from operation, with marked improvement in acromegaly.

On September 30, the patient's temperature was 97 F, pulse rate 87, weight 196 pounds (89 Kg), and B M R  $\mp$  0 per cent.

CASE 8—Miss S M, a Jewess, aged 23, was admitted to the hospital on April 22, 1926. Onset of the illness with severe headaches and enlargement of extremities had occurred at the age of 15. She did not have amenorrhea. Glycosuria was not present, but a low tolerance for sugar. The thyroid was not palpable. The pulse rate was 80. There was a slightly enlarged sella, pallor of optic disks and beginning upper bitemporal field defect.

On April 23, her height was 171 cm (5 ft, 84 in), weight 176.1 pounds (79.8 Kg), temperature 98 F, pulse rate 93, and B M R +24 per cent.

On May 10, a transphenoidal operation was performed with radical removal of eosinophilic adenoma. Convalescence was uncomplicated with marked improvement in symptoms.

On May 28, her weight was 168 pounds (76.2 Kg), temperature 99.2 F, and B M R +4 per cent. The patient was discharged from the hospital.

CASE 9—David M, a Jew, aged 36, was admitted to the hospital on June 22, 1926. The disease was of ten years' duration. He was admitted on account of increasing headaches and loss of vision. There was outspoken acromegaly with a large sella and bitemporal hemianopia. Glycosuria was not present, but low tolerance for sugar was demonstrated. The thyroid was not palpable. The pulse rate was variable, averaging 70.

On June 23, his height was 167 cm (5 ft, 68 in), weight 161 pounds (73.0 Kg), temperature 98.6 F, pulse rate 73, and B M R +16 per cent.

On July 2, a transphenoidal operation with fairly radical excision of chromophilic adenoma was performed. There was an uncomplicated recovery with marked improvement in both local and general symptoms.

On July 12, his weight was 149.8 pounds (67.8 Kg), temperature 98.2 F, pulse rate 66, and B M R +3 per cent. The patient was discharged from the hospital.

On September 24, he reentered the hospital for a metabolism test and the B M R was found to remain low, +2 per cent.

None of these nine patients showed any clinical evidence of hyperthyroidism. One of them had a palpably enlarged thyroid, but like the others did not show tachycardia, tremor or exophthalmos. It would seem, therefore, unless there is some point in the argument which has escaped us, that these cases meet the essential criteria, namely, that patients with acromegaly who have an elevated metabolic rate in the absence of clinical symptoms of hyperthyroidism show a distinct drop in the preoperative rate after partial removal of the hypophyseal adenoma, which inevitably is of the acidophilic type known to accompany hyperpituitarism.

#### SUMMARY AND CONCLUSIONS

1. Acromegaly is a disease which bears the same relation to pituitary insufficiency (hypopituitarism) that exophthalmic goiter bears to myxedema (hypothyroidism). It is, in other words, an expression of hyperpituitarism just as exophthalmic goiter is of hyperthyroidism.

2. Acromegaly is often accompanied by an elevated basal metabolic rate and the reverse condition of hypopituitarism by a subnormal rate.

3. Acromegaly, furthermore, is often accompanied by a palpably enlarged thyroid and by symptoms suggesting thyreotoxicosis to which the increased basal metabolic rate has generally been ascribed.

4 Occasionally the goiter in cases of acromegaly has been operated on under the assumption that the symptoms were due to primary hyperthyroidism. The gland in three such cases has been found to show merely colloid changes of adenomatous type without the expected evidences of toxicity. Nevertheless, thyroidectomy has served to lower the metabolic rate, and Lugol's solution has also been shown capable of lowering it.

5 On the other hand, operations on the chromophilic hypophyseal adenoma itself in cases of acromegaly in which the basal metabolism is elevated, even in the absence of a palpably enlarged thyroid, are followed by a fall in the metabolic rate almost as uniformly and strikingly as are the operations on the thyroid in exophthalmic goiter.

6 One may conclude that the chromophilic cells of the anterior lobe of the pituitary body secrete a substance which not only contains the hormone of growth, but which is capable of raising the basal metabolic rate. Whether the hypophyseal principle under these circumstances acts as a stimulus to metabolism directly on the tissues or only through the intermediation of the thyroid cannot as yet be positively stated, although there are reasons to believe that it may act independently.

7 In either event, whether the effect is primary or secondary, the elevation of the metabolic rate may properly be ascribed to the hyperpituitarism.

# ADDISON'S DISEASE AND DIABETES MELLITUS OCCURRING SIMULTANEOUSLY

## REPORT OF A CASE \*

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The combination of diabetes and Addison's disease appears from the literature to be of extremely rare occurrence. Heller<sup>1</sup> found this association only once in 800 cases of Addison's disease reviewed by him. Although there are five cases in the entire literature in which the authors state that the patients have had diabetes in conjunction with Addison's disease, the diagnosis in every one of these cases may be questioned. The only evidences of diabetes in the patient referred to by Heller were somnolency and a strongly positive reaction for acetone in the urine. Nothnagel,<sup>2</sup> who originally reported this case, referred to it merely as one of Addison's disease with severe cerebral manifestations. Of the four remaining cases, certainly that of Rabe<sup>3</sup> and possibly that of West<sup>4</sup> were instances of tuberculosis of the suprarenal glands with hemochromatosis and glycosuria. In the former case this diagnosis was proved by pathologic studies. In West's case, owing to the loss of the notes on the autopsy, accurate pathologic description is not available, however, the enlargement of the liver noted prior to death suggests the diagnosis of hemochromatosis in this case also. At any rate, the evidence presented does not warrant the diagnosis of Addison's disease, especially since mention is not made of the existence of hypotension, asthenia or gastro-intestinal symptoms. Finally, two cases<sup>5</sup> of diabetes and tuberculosis involving one or both suprarenal glands have been reported. In neither case were pigmentation, weakness, gastro-intestinal symptoms or hypotension noted. Neither could therefore be said to present the syndrome of Addison's disease.

## REPORT OF CASE

*History*—The patient, aged 39, who came under the observation of Dr. John H. Musser, Jr., at the Presbyterian Hospital, Philadelphia, for the first time on May 7, 1924, gave a history of having always been subject to headaches, but said that otherwise she had been in good health. She had married at the age of 26.

\* From the Medical Division of the University Hospital.

\* Read before the Section on General Medicine of the College of Physicians.

1 Heller, J. *Deutsche med. Wchnschr.* **33** 1216 (July 25) 1907.

2 Nothnagel, H. *Ztschr. f. klin. Med.* **9** 195, 1885.

3 Rabe, M. *Bull. et mem. Soc. anat. de Paris* **75** 459 (May) 1900.

4 West, S. *Tr. Path. Soc. London* **41** 271, 1890.

5 Montgomery, C. M. *A Case of Diabetes Mellitus Associated with Tuberculosis of the Adrenal Glands*, *J. A. M. A.* **58** 847 (March 23) 1912.  
Ogle, J. W. *St. George's Hosp. Rep.* **1** 178, 1866.

and had had five pregnancies, one being a two months' miscarriage, one child had died of pneumonia in infancy. The remaining three children were healthy. There was no history of severe illness or abdominal trauma which might explain simultaneous pancreatic and suprarenal disease, nor was there any history of exposure to silver or any other metal to account for the generalized pigmentation. She spent the summer of 1923 at the seashore, and was, as she believed at the time, tanned by exposure to the sun. After returning to the city, the color of her skin remained dark, and as the winter progressed, instead of becoming lighter, it became darker. About December, 1923, she began to complain of weakness, loss of energy, nausea and exacerbation of the headaches. For these symptoms she consulted an ophthalmologist and a dentist, who did not find anything abnormal. She began to lose weight, and about April 23, 1924, polyuria, polyphagia and polydipsia made their appearance. On May 5, she was so weak that she was forced to remain in bed. She was nauseated and vomited all that night.

*Examination*—Sugar was found in the urine. A diagnosis of diabetes was made, and the patient was sent to the Presbyterian Hospital under Dr. Musser's care. At this time she was drowsy, could be only partially aroused and could not answer questions. Her blood sugar content was 0.44 per cent, and she was obviously in a state bordering on coma.

*Treatment and Course*—During the first twenty-four hours she was given 293 Gm of carbohydrate in the form of glucose by rectum, orange juice and glucose by mouth and 100 units of insulin. The specimen of urine contained 7.2 Gm of sugar for this day, but some may have been lost, for on the following day 22.5 Gm were passed, 75 units of insulin being given. At this time the patient weighed 99½ pounds (45.1 Kg), 20 pounds (9 Kg) under her usual weight. In five days the urine became sugar-free and continued so for the remainder of the patient's stay in the hospital. She suffered three insulin shocks during the period of her stay, these occurred on days when she received, respectively, 80, 80 and 50 units of insulin and 60, 40 and 40 Gm of carbohydrate. She was discharged from the hospital on June 11, 1924, feeling well, taking 20 units of insulin before breakfast, 10 units before lunch and 20 units before supper. Her diet at this time consisted of 55 Gm of protein, 160 Gm of fat, and 90 Gm of carbohydrates. On this regimen she felt well, and in six months gained 21 pounds (9.5 Kg) although sugar was present in her urine at times. From this time on glycosuria gradually became more and more difficult to control, and when, on Dr. Musser's leaving Philadelphia, she came under my observation, specimens of her urine contained sugar much of the time.

On Oct. 10, 1925, her urine contained diacetic acid and vomiting commenced. She entered the University Hospital. Her blood sugar on admission was 0.255 per cent and the carbon dioxide content of her blood plasma was 35 per cent by volume, under treatment, four days later, this figure rose to 54. The urine was pale yellow, clear, acid, had a specific gravity of 1.020, contained a normal number of leukocytes but no albumin, casts, cylindroids or erythrocytes. The blood count showed erythrocytes, 3,750,000, leukocytes, 7,900, hemoglobin, 69 per cent (Sahli), neutrophils, 45 per cent, lymphocytes, 49 per cent and monocytes, 6 per cent. The temperature was 99.2 F, the pulse rate 100, and the respiratory rate 18 per minute. Physical examination showed a woman, 5 feet, 3 inches in height, weighing 109¼ pounds (49.5 Kg). The surface area was estimated as 1.5 square meters and the basal requirement as 1,300 calories per day. The shape and configuration of the body were normal and in no way suggested polyglandular disease. She could stand with difficulty because of weakness. The entire body was pigmented, resembling somewhat the tint of ordinary seashore tan, but more nearly that shown in the illustrations at the end of Addison's monograph.<sup>6</sup> The face and dorsal aspect of the hands were somewhat darker than the rest of the body, but no part was free from pigmentation. The buccal mucous mem-

<sup>6</sup> Addison, T. On Disease of the Suprarenal Capsules, London, 1855.

brane was not pigmented (such lack of pigmentation is by no means uncommon in Addison's disease) The rectum and vagina were not examined The brachial arteries were soft, a striking characteristic of the physical examination was the low tension of the radial pulse The blood pressure was systolic, 95, diastolic, 72 Examination was otherwise normal Neither the liver nor the spleen was palpable Each specimen of urine was tested (generally by the patient) for sugar and diacetic acid Of 344 such tests made during her forty-seven days' stay in the hospital, sugar was present seventy-seven times and diacetic acid thirty-one times

A noteworthy feature of the case, and one constituting a problem from the therapeutic standpoint, was the patient's peculiar response to insulin She was so susceptible to this substance that she developed hypoglycemic symptoms on several occasions when 2, and even 1 unit more than her usual dosage was administered at midnight On the other hand, glycosuria would occur on the slightest provocation, and if allowed to go unchecked was soon followed by vomiting and the appearance of diacetic acid in the urine Hypoglycemia manifested itself first by mental dulness If it occurred during sleep, she would be difficult to awaken, and after awakening would be slightly disoriented If hypoglycemia occurred during the day, she would become mentally dull and forget-

### Blood Sugar Readings\*

Date	Blood Sugar, Per Cent	Glycosuria	Insulin, Units	Food Grams			Time
				Protein	Fat	Carbohydrate	
Oct 27, 1925	0.842	+	25	4	9	10	Breakfast
	0.077	—	0	15	19	10	Lunch
	0.082	—	5	22	28	14	Supper
	0.030†	—	0	0	0	10	Midnight
Oct 29 and 30, 1925	0.063	—	10	22	28	14	Supper
	†	—	0	0	0	10	Two hours later
	0.071	—	5	0	0	0	2 a m
	0.139	—	15	4	9	10	Breakfast
	0.030†	—	0	15	19	10	Lunch

\* Blood was taken before injection of insulin or meal, insulin was given twenty minutes before specified meals

† Slight hypoglycemic symptoms

ful Although ordinarily bright and intelligent, she never learned to recognize hypoglycemia, and would eat her lump of sugar only when ordered to do so That these symptoms were actually due to hypoglycemia was proved on a number of occasions by obtaining blood sugar readings of less than 0.04 per cent during such attacks During this stay in the hospital thirty-two mild hypoglycemic reactions occurred, and twice she had severe reactions in which she became unconscious and was given epinephrine hydrochloride On both occasions, consciousness returned before glucose could be given intravenously

Many blood sugar determinations were made during her stay in the hospital, the readings secured ranging from 0.423 to 0.03 per cent The figures for two series of such determinations covering twenty-four hours each are shown in the table

A regimen was finally evolved on which she gained weight, and remained sugar-free, shock-free and ketone-free It consisted in a daily allowance of 57 Gm of protein, 187 Gm of fat and 57 Gm of carbohydrate (2,139 calories a day), with 10 units of insulin twenty minutes before breakfast, 5 units twenty minutes before supper and 5 units at 3 a m On following this schedule, she went home, able to walk and feeling greatly improved

*Second Admission to Hospital*—On Jan 15, 1926, she again returned to the hospital, this time because of extreme weakness Her blood sugar was 0.193 per cent, the blood urea nitrogen 24 mg per hundred cubic centimeters of blood and the carbon dioxide content of the plasma 51 per cent by volume Fifteen

grams of sugar was excreted in the urine in twenty-four hours. Acetone was present in the urine, but no diacetic acid. The blood count showed erythrocytes, 4,800,000, leukocytes, 13,000, hemoglobin, 86 per cent (Sahli), neutrophils, 46 per cent, lymphocytes, 47 per cent, monocytes, 2 per cent, and eosinophils 5 per cent. Results of physical examination were essentially the same as on the previous admission except that the patient was weaker than before, and that the pigmentation had become noticeably deeper. The blood pressure varied from 90 systolic and 66 diastolic to 78 systolic and 55 diastolic, showing little variation attributable to meals or injections of insulin, 30 mg of ephedrine<sup>7</sup> taken by mouth also failed to raise the blood pressure. The pulse rate varied from 80 to 108 and respirations from 17 to 20 per minute. The temperature was subnormal. Vomiting commenced on January 17. She grew weaker, diacetic acid as well as acetone appeared in the urine. Two days later, cough and pain in the chest appeared. At 6 a m, January 20, she complained of difficulty in breathing and severe pain in the chest. She became unconscious and died suddenly.

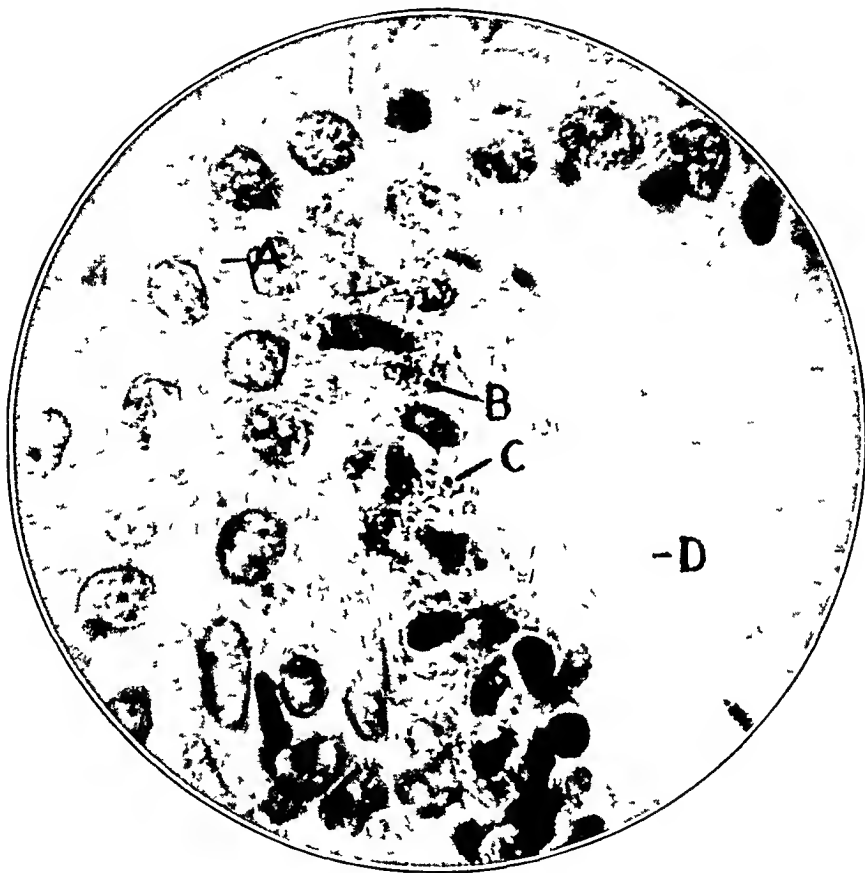
*Autopsy*—This was performed five and one-half hours after death by Dr Morton McCutcheon, assistant professor of pathology. Interest centered chiefly in the suprarenal glands; a prolonged search by Dr McCutcheon and others failed to reveal the slightest trace of the suprarenal gland on the right side, one piece of tissue was removed on suspicion, but on section it exhibited no semblance of suprarenal structure. The suprarenal gland on the left side was readily found and measured 15 by 35 by 5 mm, the cortex was white, the medulla was mottled pink and gray, its appearance did not suggest tuberculosis. On microscopic examination, it showed a normal capsule, there was, however, a marked increase in connective tissue, the latter being of adult type chiefly. Lymphocytic infiltration was extensive, due to these changes, the architecture of the gland was indistinct, and in most parts the cortical cells were small and devoid of lipid. Islands of large cells were found at the periphery, these also were devoid of lipid.

The anatomic observations in the other organs were as follows: the pancreas weighed 60 Gm and measured 20.5 by 3 by 1.5 cm, it was not pigmented or fibrotic as in hemochromatosis, but flaccid and normally lobulated. The liver also was normal in consistency and without any sign of cirrhosis. It weighed 1,360 Gm, and its capsule was transparent, on section it was dark brown and showed indistinct nutmeg markings. The gallbladder and bile ducts were normal. The pleural cavities were free from fluid or adhesions, and the pericardial sac was normal. The heart weighed 230 Gm, the epicardium was smooth, and the myocardium dark brown, slight thickening of the mitral valve was present. Culture of the heart blood showed *Bacillus coli communis*. The lungs were pale and somewhat watery on section, otherwise normal. The stomach, esophagus and intestines were normal. The spleen weighed 120 Gm, was of normal consistency and on section showed normal color and markings, its capsule was not thickened. The kidneys weighed 140 Gm each and were of normal consistency, on section, the left kidney was congested, the right pale. Both ureters were normal, as were also the internal and external genitalia.

On microscopic examination, the pancreas showed a slight increase in the interlobular fibrous tissue, no pigments were present, both acini and islets appeared somewhat smaller than usual, and the latter were numerous and contained some small, poorly staining cells and also some large cells with deeply staining nuclei. The liver capsule and interlobular structures were normal, the liver cells appeared swollen and rarefied, with nuclei swollen or poorly staining. These changes were less marked toward the periphery of the organ, the cells in the vicinity of the capsule often appearing normal, greenish-brown pigment of finely granular character was found rather abundantly, chiefly in the hepatic cells of the central lobular region. This pigment did not react for iron, Kupffer cells were not conspicuous, and there was no evidence of hepatic cirrhosis. The cap-

<sup>7</sup> Miller, T G. Am J M Sc 170 157 (Aug) 1925

sule of the spleen was not thickened, and the trabeculae were normal, the splenic follicles were numerous and slightly enlarged. The only noteworthy change in the kidneys was an increase in the interstitial tissue of the subscapular region, associated with lymphatic infiltration. The sections of the lung were essentially negative. In the thyroid the interstitial tissue was normal, the acini varied considerably in size and were filled with colloid, hyperplastic changes were not present. A section of the skin of the abdomen (fig 1) showed marked pigmentation of the stratum germinativum comparable to that found in negroes. The pigment did not give a reaction for iron.



Abundant deposition within the skin of large pigment granules which gave a negative reaction for iron. *A* indicates the stratum germinativum, *B* and *C*, pigment granules, *D*, corium.

#### COMMENT

Bronzed diabetes must of course be considered here as a possible explanation for the pigmentation and glycosuria. This disease known since von Recklinghausen's<sup>8</sup> time as hemochromatosis with glycosuria, and before this as the cirrhose hypertrophique pigmentaire of Hanot and Chauffard,<sup>9</sup> is characterized by cirrhosis of the liver, sclerosis of the pancreas and other organs and the presence of a pigment reacting to iron,

<sup>8</sup> Von Recklinghausen. *Tageblatt der 62. Versammlung Deutscher Naturforscher und Aerzte in Heidelberg, 1889*, p. 324.

<sup>9</sup> Hanot, V., and Chauffard, A. *Rev. de med.* 2: 385, 1882.

none of which this case exhibited. On the other hand, in addition to presenting the characteristic clinical and chemical picture of diabetes mellitus, the pigmentation, vomiting, excessive hypotension and asthenia in this case presented an unmistakable picture of Addison's disease.

The pathologic observations pointed to an old inflammatory process involving both the islands of Langerhans and the supra-renal glands, with evidences of attempts at regeneration in<sup>10</sup> both. The etiology of this process remains obscure. From the history it would appear that the involvement of these two structures occurred simultaneously, and this view was confirmed at autopsy.

The hypersensitivity to insulin which this patient manifested to an increasing extent, especially during the last weeks of her life, can best be explained on the basis of diminished supra-renal function. That such hypersensitivity may be caused by supra-renal insufficiency is proved by the fact that the administration of insulin to supra-renalectomized animals,<sup>11</sup> or to persons with Addison's disease, is known to produce hypoglycemia out of all proportion to that which occurs when the supra-renals are functioning normally. For example, Marañon<sup>12</sup> reports the case of a woman, aged 40, with Addison's disease, who suffered severe hypoglycemic symptoms following the administration of 10 units of insulin hypodermically, while in another case of Addison's disease occurring in a girl of 16, death followed the administration of 5 units of insulin.

Of especial interest to the student of endocrinology is the fact that in this case there was an insufficiency of two "antagonistic" glands, namely the islands of Langerhans and the supra-renals. This so-called antagonism refers to the glycemic action of the two respective hormones, and finds its practical application in the use of epinephrine hydrochloride in insulin shock. This usage is based on the fact that the hypodermic injection of epinephrine raises<sup>13</sup> while insulin lowers<sup>14</sup> the blood sugar. On the other hand, when an insufficiency of these hormones is present, the opposite state of affairs exists, namely, in supra-renal insufficiency (Addison's disease) the blood sugar is low,<sup>15</sup> while in insufficiency of the islands of Langerhans (diabetes) the blood sugar is high. Based on these considerations, destructive radiation of the supra-renal glands has

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10 Boyd, G., and Robinson, W. L. *Am J Path* **1** 135 (March) 1925.  
Warren, S., and Root, H. F. *Ibid* **1** 415 (July) 1925.

11 Hallion, L., and Gayet, R. *Compt rend Soc de biol* **92** 945 (April 3) 1925.  
Sundberg, C. G. *Ibid* **89** 807 (Oct) 1923.

12 Marañon, G. *Presse méd* **33** 1665 (Dec 19) 1925.

13 Blum, F. *Deutsches Arch f klin Med* **71** 146 (Oct) 1901.

14 Banting, F. G., Best, C. H., Collip, J. B., Campbell, W. R., and Fletcher, A. R. *Canad M A J* **12** 141 (March) 1922.

15 Poiges, O. *Ztschr f klin Med* **69** 341. 1910.

been practiced in the treatment of diabetes mellitus<sup>16</sup> The published data, nevertheless, do not indicate any striking results either in curing the diabetes or in producing Addison's disease Judging, however, from the clinical course of the case here reported, the destruction of the suprarenal glands by any agency could scarcely be regarded as a safe or desirable form of treatment for diabetes mellitus

#### SUMMARY

The combination of Addison's disease and diabetes mellitus is extremely rare It is moreover of great interest, because the two ductless glands involved, namely, the suprarenals and the islands of Langerhans, secrete hormones producing opposite glycemic effects The case herewith reported presented both the clinical and chemical evidences of diabetes mellitus, together with the pigmentation, asthenia, low blood pressure and vomiting which are characteristic of Addison's disease Autopsy bore out this diagnosis Unusual therapeutic difficulties were encountered owing to the existence of a hypersensitivity to insulin and a marked tendency to ketosis, the former no doubt being due to suprarenal insufficiency

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<sup>16</sup> Dresel, K *Deutsche med Wchnschr* **46** 1240 (Nov 4) 1920 Beumer, H *Ibid* **47** 369 (March 31) 1921

# CONGENITAL VENTRICULAR SEPTAL DEFECT IN A MAN, AGED SEVENTY-NINE \*

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Ventricular septal defects are usually situated just beneath the aortic cusps, anterior to the undefended space, and are frequently associated with other anomalies, such as pulmonary stenosis and dextroposition of the aorta. Rarely do they occur alone. The following case is unique in the peculiar location and large size of a congenital ventricular septal defect unassociated with other anomalies. The age of the patient and the absence of cardiac symptoms other than a terminal cyanosis are additional features of interest.

## REPORT OF CASE

*History*—H F, a white man, aged 79, an inmate of the Old Folks Home of the Jewish Hospital, whose chief complaint was stomach trouble, was admitted to the medical ward in the service of Dr S Solis Cohen, May 4, 1926. His family history was unimportant. At the age of 40 he had had typhoid fever, and at the age of 64 he had dislocated his right knee joint, the dislocation had persisted, making it necessary for the patient to use crutches. For twenty years he had suffered from severe shooting pains down the thighs and legs posteriorly, these pains occurred in attacks which lasted for two or three days at a time. Other than the aforementioned difficulties, the patient had been in good condition and had felt well until about two and one half weeks before his admission to the hospital. At this time an attack of sciatica occurred, accompanied by nausea, which caused the patient to vomit on several occasions. He never had had shortness of breath, swelling of the legs, palpitation or cardiac pain. On admission to the hospital his temperature was normal, the pulse rate varied between 80 and 90, and his respiration was normal.

*Physical Examination*—This showed an aged white man, fairly well nourished, lying quietly in bed, with marked cyanosis of the hands and feet. There was some engorgement of the veins of the neck, and examination of the heart revealed striking signs. At the ensiform cartilage there was an intense systolic thrill, and a loud, harsh systolic murmur. The murmur could be heard all over the cardia, but was loudest at the ensiform cartilage. The aortic and pulmonary second sounds were not accentuated. It was difficult to outline the heart borders, but there did not seem to be an enlargement either to the right or to the left. Examination of the abdomen showed the liver edge palpable two fingerbreadths below the costal margin, but it was not tender. The spleen was not palpable, evidence of ascites was not found. Examination of the extremities showed the old dislocation of the right knee, and, as mentioned in the foregoing, marked cyanosis of the hands and feet.

*Diagnosis*—At first sight this seemed to be either a tricuspid or a mitral lesion, but the history did not denote mitral disease, the aforementioned murmur and thrill were the only indications of this form of valvular disturbance. Against a tricuspid lesion sufficiently severe to produce such pronounced physical signs, was the absence of the phenomena of failure of the right side of the heart, edema was not present, nor was there marked enlargement of the liver—the clinical picture was not that of congestive heart failure.

\* From the Medical Service of Dr S Solis Cohen, Jewish Hospital.

The unusual position of the intense thrill and the harsh quality of the murmur, together with the peculiar cyanosis, suggested the possibility of a latent congenital lesion, such as a septal defect, this was the probable diagnosis made, but it was not possible to say whether the defect was between the auricles or between the ventricles

The course of the illness was steadily downward. The patient developed urinary retention, finally refused to take food and died on May 31. He did not show signs at any time of congestive heart failure. Urinalyses had consistently shown heavy traces of albumin, white blood cells and occasional hyaline casts. The blood count showed a moderate degree of anemia, with 20,000 leukocytes, 80 per cent of which were polymorphonuclear neutrophils. The blood pressure was systolic, 100, diastolic, 80, and remained at about this level. The blood Wassermann reaction was negative. At the time of admis-



Fig 1—Congenital ventricular septal defect situated in the posterior half of the septum, midway between the apex and the mitral orifice. There were not any associated anomalies.

sion, the blood urea nitrogen was 90 mg, which was ascribed to the urinary retention. With forced fluids and catheterization, it dropped to 23 mg.

The electrocardiogram, taken two days after admission, showed a rate of 84, irregular from auricular premature beats. The auriculoventricular bundle conduction was normal. The right branch bundle conduction was impaired, with delay. There was evidence of right ventricular preponderance and myocardial degeneration.

*Autopsy*—Postmortem interest was centered in the heart. Other than marked sclerosis of the kidney and chronic cholecystitis, there was nothing unusual about the appearance of the other organs.

The heart weighed 370 Gm. and appeared normal in size. The surface of the visceral pericardium was somewhat roughened with fine shreds of fibrin, representing a terminal fibrinous pericarditis. The muscle of the left ventricle was

1.5 cm in thickness, firm in consistency and showed minute patches of fibrous tissue. The muscle of the right ventricle was 0.4 cm in thickness. The right side of the heart appeared somewhat dilated, containing blood clot. The tricuspid orifice was 1.3 cm in circumference, the valve cusps appeared normal. The pulmonary orifice was 8.5 cm in circumference, these cusps were likewise normal. The aortic orifice was 9 cm in circumference, the aortic leaflets were somewhat thickened and sclerotic, and the aortic arch, with the exception of the first portion, was markedly sclerotic. The openings of the coronary arteries were somewhat narrowed, and the coronary vessels throughout their course were generally thickened. The mitral orifice was 10 cm in circumference, the cusps were slightly thickened, and there was a large atheromatous plaque in the posterior leaflet.

The striking feature of the heart was the large defect of the interventricular septum situated in the posterior half of the septum, about midway between the

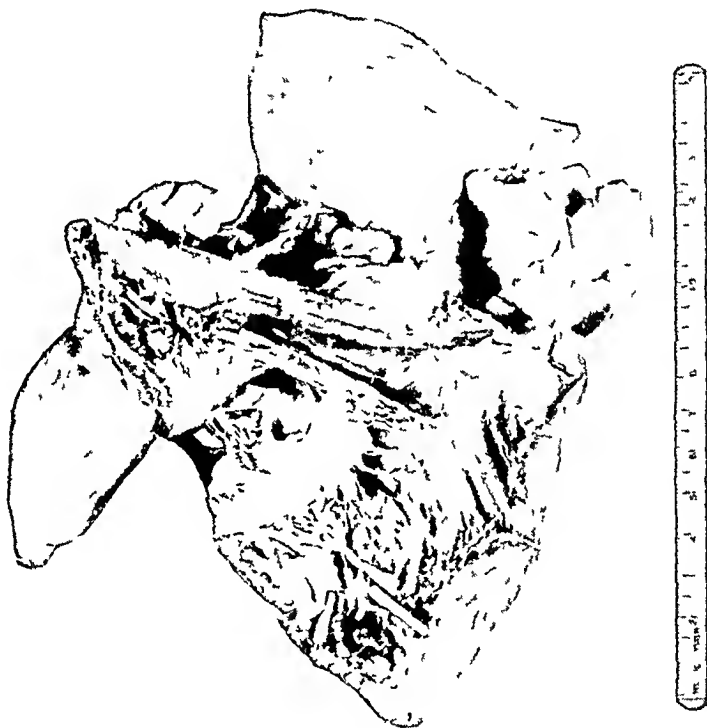


Fig 2—Right side of the heart showing openings of septal defect between the muscle columns near the apex. White rods are passed through two of the openings.

apex of the left ventricle and the mitral ring (fig 1). The defect was circular in outline, measuring 2 cm in diameter, and communicated with the right ventricle near the apex by means of an aneurysmal pouch with fenestrated openings. This pouch was 2.5 cm in depth, and was large enough to accommodate a good sized olive. The edge of the defect on the left side of the heart was fibrous and smooth. The openings in the right ventricle were four or five in number, occurring between the columna carnea near the apex of the right ventricle (fig 2). Directly above the defect and just below the mitral orifice was a roughened spot where thrombus material was attached.

The location of the defect, its large size, the smooth, fibrous edge, the aneurysmal communication with the right ventricle and the natural openings between the muscle columns near the apex of the right ventricle were features which distinguished this as a congenital lesion.

## COMMENT

Ventricular septal defects belong to that group of cardiac anomalies which are unassociated with cyanosis, except as a transient or terminal event. Comprising this group are patent ductus arteriosus, direct communications between the aorta and the pulmonary artery, defects of the auricular septum and defects of the ventricular septum. With any such anomaly, I believe, from morphologic evidence, that the flow of blood is from the side in which the pressure is higher, that is, systemic circulation, into the side in which the pressure is lower, or the lesser circulation. In other words, the flow of blood is from the left to the right, or what has been termed by Abbott<sup>1</sup> as arteriovenous shunt. Under such circumstances there is not a cause for cyanosis, and the only pathologic factor at work is a slowly developing strain, manifested by hypertrophy of the walls and by fibrosis in the region of the defect. If, because of heightened tension on the pulmonary side, or weakening of the systemic circulation, a reversal of the shunt occurs, that is, the blood flow is from the venous to the arterial side instead of from the arterial to the venous, cyanosis occurs, this may be transient or terminal, constituting what the French have termed "cyanose tardive."

It is probable that such was the case in the present instance. All through life the defect did not interfere in any way with good cardiac function, the shunt of blood was probably from the left to the right. During the last days of life it is probable that a reversal of the shunt occurred sufficient to produce cyanosis.

The diagnosis of cardiac defects belonging to this so-called non-cyanotic group usually does not offer any great difficulty. The presence of striking physical signs and the absence of cardiac symptoms are characteristic features. A peculiar harsh murmur of unusual rhythm and intensity, often accompanied by a thrill, situated to the left of the sternum in the first or second interspace, or over the middle of the precordium, and in many instances associated with evidences of dilatation of the pulmonary artery, are the most important diagnostic features of this noncyanotic group. Such physical signs in a person without a history of rheumatic fever or other illnesses commonly causing endocarditis, readily permit a diagnosis of a congenital defect belonging to this group.

The problem, then, is to differentiate the type of lesion, and this is often possible, depending on the distinctive physical signs of the various defects.<sup>2</sup>

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1 Abbott, M. E., and Dawson, W. T. The Clinical Classification of Congenital Cardiac Disease, *Internat Clin* 4 155, 1924.

2 Abbott and Dawson (footnote 1). Weiss, Edward. The Differential Diagnosis of Congenital Heart Disease, *M Clin N Am*, Philadelphia number 10 185 (July) 1926.

In the case under discussion, the advanced age of the patient seemingly was against a congenital lesion, but the distinctive quality and unusual position of the harsh murmur and intense thrill, without the history or physical indications of an acquired lesion, and without evidence of congestive heart failure, led to the conclusion that in this case the lesion was congenital probably a septal defect. Whether this defect was between the auricles or between the ventricles, the location of the murmur and thrill did not permit us to say. The further conclusion that a right to left (terminal) shunt had occurred, and that the flow of blood through the defect was probably from the venous to the arterial side could be drawn from the presence of a peculiar deep cyanosis of the hands and feet.

Perhaps the most interesting feature of this case report is the rarity of the type of defect. As mentioned before, defects of the ventricular septum usually occur at the base and are readily explained on the basis of an arrest of development, particularly in their common association with other anomalies of the pulmonary conus and great vessels.

The defect under discussion occurred in an extraordinary position, and I am unable to find any recorded similar cases, in which such a large defect occurred in this location unassociated with other anomalies. Dr. Abbott,<sup>3</sup> whose knowledge of the subject of cardiac anomalies is authoritative, states that the present case is unique. She suggests in explanation of its formation that, from a comparative standpoint, a homologue can be found in the heart of the python, in which a communication exists low in the septum between the dorsal and ventral ventricles.<sup>4</sup>

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<sup>3</sup> Personal communication to the author.

<sup>4</sup> Abbott, M. E., and Stanley, Eleanor. Cardiac Defects in the Light of the Comparative Anatomy of the Vertebrate Heart, *Bull. Internat. A. M. Museums* 8: 1-32 (Dec.) 1922.

# SOME CONDITIONS AFFECTING SUBJECTIVE AND OBJECTIVE MANIFESTATIONS OF HUNGER \*

HUNGER SENSATION GIVING RISE TO A MARKED  
RESPIRATORY CHANGE

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AND  
NATHANIEL KLEITMAN  
CHICAGO

While making simultaneous observations on gastric motility (by the balloon method) and on the basal metabolic rate (Kleitman),<sup>1</sup> a striking increase in the respiratory rate was manifested during some periods of gastric hunger contractions (fig 1). The increase was recognized by the subject (F. H.) as accounting for his previous belief that the metabolic rate was increased with hunger contractions. This belief occasioned the investigation but was based mainly on subjective experience, particularly during a thirty-three day fast undertaken some time previously. However, similar subjective experience during earlier fasts had already led to a study of this problem by Dr. Kunde (unpublished work). She made observations on a number of subjects, but did not obtain conclusive evidence of an increase in the basal metabolic rate with increases in gastric motor activity. This observation was confirmed by Kleitman. Kunde, however, did not note the striking increase in the respiratory rate which we observed, although she found that minor and irregular changes in respiration occurred. None of Kunde's subjects fasted more than five days during her study, while our own investigation did not begin until the twenty-third day of a forty-one day fast.

The fact that neither Kunde's nor Kleitman's study revealed an increase in the basal metabolic rate during periods of hunger contractions indicates that the increased respiratory rate was not due to greater need of oxygen. Apparently, it was reflexly induced by the hunger sensation. The increase in the respiratory rate was accompanied by a simultaneous decrease in the depth of the respiratory excursions. Whether the increase in rate or the decrease in depth was primary is an unsettled question. If it were the latter, this phenomenon would be comparable to the reflex rigidity of the abdominal muscles which is frequently manifested with intra-abdominal lesions. But, instead of the abdominal muscles contracting, the contractions of these muscles and of the diaphragm seemed to be inhibited. That is, an increase in intra-abdominal pressure apparently was reflexly prevented to avoid an

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\* From the Hull Physiological Laboratory of the University of Chicago.  
1 Kleitman, N. *Am J Physiol* **77** 233, 1926

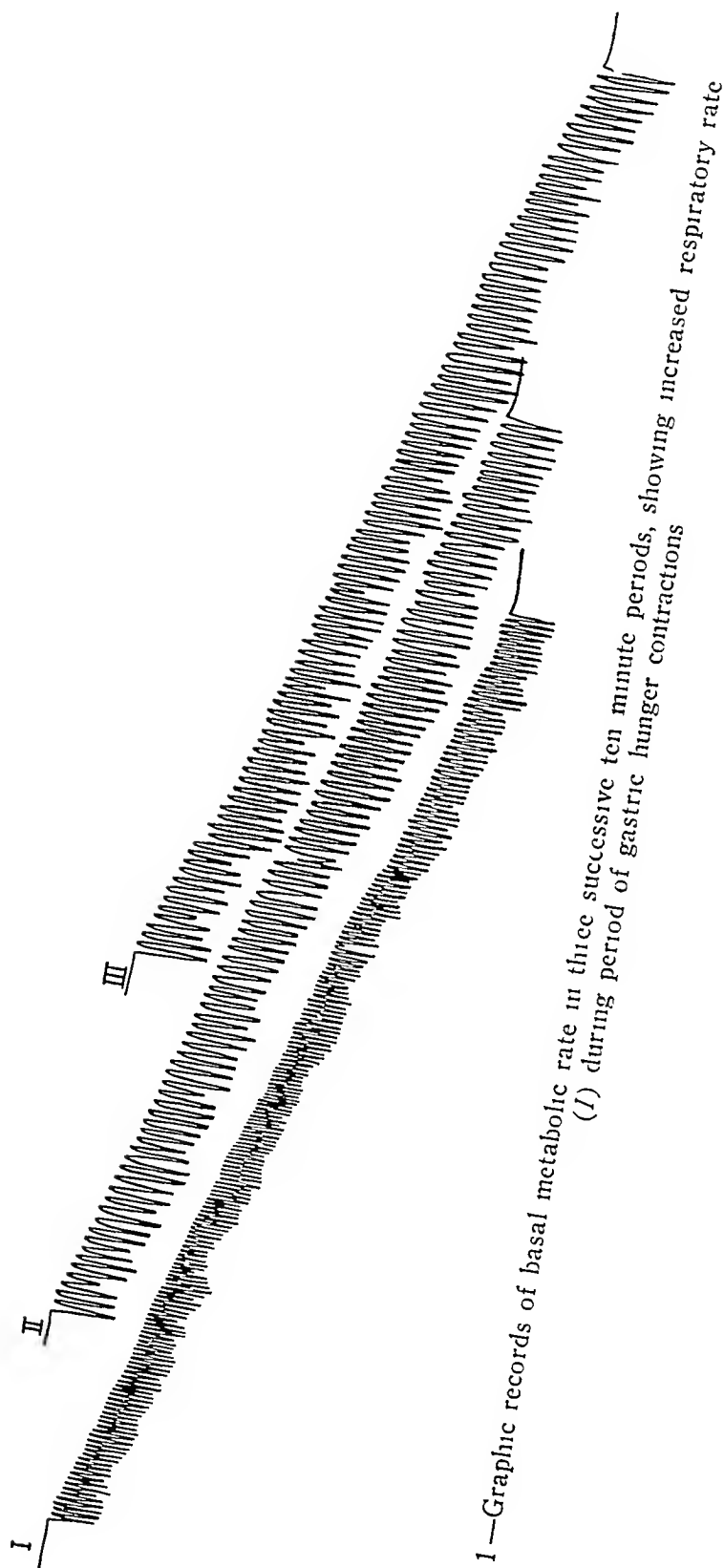


Fig 1—Graphic records of basal metabolic rate in three successive ten minute periods, showing increased respiratory rate (I) during period of gastric hunger contractions

increase in the hunger pain. However, as it was not the change in depth but rather the increase in the respiratory rate which was most obvious, this increase will chiefly be referred to, for descriptive purposes, in what follows.

Occasionally, the metabolic graphs showed a considerably increased respiratory rate somewhat independent of the individual hunger contractions, and also at times when the subject thought that his rate had been normal. This raised the question as to whether we were not dealing with an artefact caused by the construction of the metabolic apparatus. At least, it seemed possible that a change in the type of respiration might be reflected as an increase in the rate because of the interference with natural breathing occasioned by the apparatus. For instance, the gas exchange in the apparatus used (Sanborn-Benedict type) occurs about

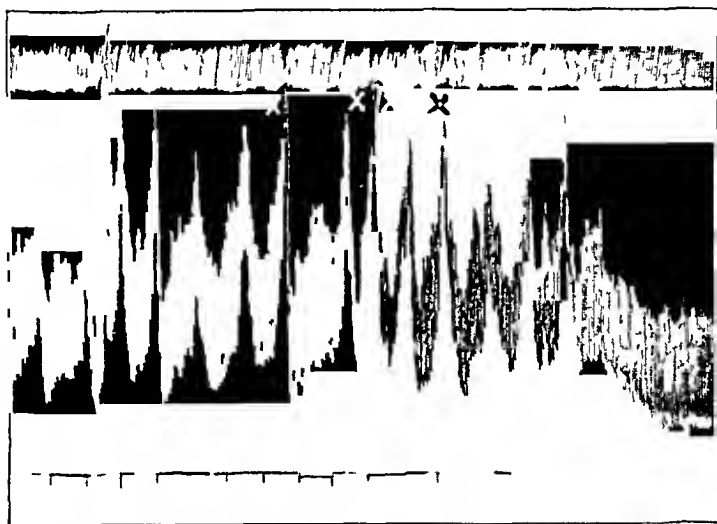


Fig 2—Period of gastric hunger contractions (middle tracing). The upper tracing is a pneumograph record showing intermittent increases in respiratory rate (X, X, X), time is given in minutes below.

10 cm from the subject's mouth. This makes an increased dead space which, while perhaps of no consequence under normal conditions, might have to be taken into consideration when respiration is altered, during fasting, under nutrition and other conditions. Observations were therefore made (after the forty-one day fast) without the metabolic apparatus, using a pneumograph, tied around the abdomen, in its place. Increases in the respiratory rate nevertheless occurred, but the increases were not, as a rule, so continuous (fig 2) as they appeared on the metabolic graphs (fig 1). The increases also agreed better with subjective sensations. Observations were also made without the balloon in the stomach and without the pneumograph, and again, although naturally with some difficulty, it was possible to recognize distinct increases in the respiratory rate on some occasions while subjectively experiencing hunger sensations.

This respiratory reflex had not been observed in the extensive work of Carlson<sup>2</sup> on hunger. It seemed possible to explain this at first by the fact that the curves of the gastric contractions tend to obscure the rate of respiration on the usual graphs. That is, a simultaneous independent record of respiration with the pneumograph or metabolic apparatus seemed necessary to bring this phenomenon to light. However, Carlson had used such methods in his investigations, and in our study it became clear before long that the condition of the subject, rather than the mode of observation, determined the results. In this connection, it is interesting to note that the subject (F. H.) failed to recognize the increased respiratory rates before our objective evidence was obtained—this, in spite of the fact that he had, at different times, fasted a total period of about three hundred and fifty days before the present experiment. That, among other things, argues against the possibility that the respiratory changes were caused by conscious attention to breathing. During most of the longer fasts, F. H. experienced "air hunger," which was attributed to acidosis. It seems possible, however, that the "air hunger" was the respiratory reflex which may, at the same time, have been accompanied by some degree of true air hunger incident to acidosis. The belief that the basal metabolic rate was increased with the periodic contractions, nevertheless, did not rest on the experience of air hunger during fasting, but was more directly based on the experience of considerable restlessness during some hunger periods.

As indicated in figure 2, the respiratory increases were usually intermittent. Respiration increased synchronously with a specific type of hunger sensation which often paralleled, but was sometimes more or less independent of, the gastric hunger contractions. With this sensation, an increased sense of tension in the gastric region was generally thought to be felt, but increases in neither the gastric tonus nor gastric contractions could account for it. This and other evidence indicated that the sensation must have come from a site beyond the position of the balloon if, indeed, it was at all caused by contractions or increases in tonus. The lack of a direct relation between the gastric contractions and the hunger sensation with the change in the respiratory rate was emphasized when the phenomenon gradually disappeared by the end of the fourth month after the forty-one day fast. About this time, the gastric periods became somewhat less frequent, but no other change, either in gastric tonus or contractions, could account for the disappearance of the sensation with the peculiar respiratory responses.

We then attempted to reestablish this hunger sensation, as we wished to study its manifestations further. F. H. had increased his carbohydrate intake a little about the time that the increases in the res-

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<sup>2</sup> Carlson, A. J. *Am. J. Physiol.* **31** 151, 1912, *ibid.* **31** 175, 1913, *The Control of Hunger in Health and Disease*, Chicago, 1916.

piratory rate became less prominent. Moreover, it was thought that acidosis or carbohydrate deficiency during fasting might have initiated the phenomenon by affecting the respiratory center. Hence, it was believed that the reflex would again become evident with carbohydrate restriction while the protein intake was kept practically constant. This, however, did not prove to be the case, even when some meals did not contain any carbohydrate and when the hunger contractions were more intense than usual. After that the effect of the use of liberal quantities of carbohydrate was observed. The respiratory rate was then found to be even less inclined to increase than with carbohydrate restriction. It should be said here that a small (from 10 to 25 per cent) increase in the respiratory rate was nearly always observed during periods of hunger contractions, but the increase which we accepted as evidence of the specific hunger sensation was an increase of about 100 per cent or more, it was sometimes as high as 200 per cent.

Since we had failed to reestablish the hunger sensation with the change in the respiratory rate by altering the carbohydrate and fat ratio in the diet, our attention was directed to the protein intake. The proportion of protein used was not considered in the first instance, because wide variations had been made previously without any obvious effect on the respiratory reflex. About the time that the evidence of the respiratory increase disappeared, a more or less constant and slightly high protein intake had been instituted. Protein was therefore reduced to create a degree of protein starvation (from 15 to 25 Gm daily being used), while other food was kept adequate. Within two days the hunger sensation with the accompanying respiratory reflex showed signs of returning, that is, when hunger sensations developed, the subject felt as if they would presently "take the breath away," although objective evidence did not indicate that. After three more days, however, increases in the respiratory rate became evident on the graphs, these increases had been absent for a month and had occurred clearly only once during the preceding two months. These results again show that the peculiar hunger sensations and the respiratory changes were not produced by conscious attention, for they did not return when they were most expected—with carbohydrate restriction. The surprisingly quick effect of protein restriction at this time was probably due to the fact that a partial decrease in the protein intake preceded the more rigid restriction. Notwithstanding the previous inability of the subject to recognize clearly the circumstances under which the hunger sensation with the respiratory increase arose, it now became evident that this sensation invariably developed with protein starvation. Its manifestation during a few short periods of excessive protein intake, within the first four months after the forty-one day fast, had somewhat obscured the relationship, with the prefasting conditions apparently restored.

however, the subject realized that it was this hunger sensation which always made prolonged protein restriction, beyond a certain point, practically intolerable. This became clearer with further experimentation, for it was then found that, after the fourteenth day of protein restriction, this hunger sensation was also manifested during motor quiescence of the empty stomach and even during digestion (fig 3). The sensation, nevertheless, was usually more distinct during the periods of hunger contractions than at other times.

Some of the observations were so unexpected that the question arose as to whether anticipation of the sensation might not, at least in some instances, give rise to the increases in the respiratory rate. As a result of some tests, it proved possible to reproduce brief respiratory increases by imagining the conditions under which they occurred and adjusting

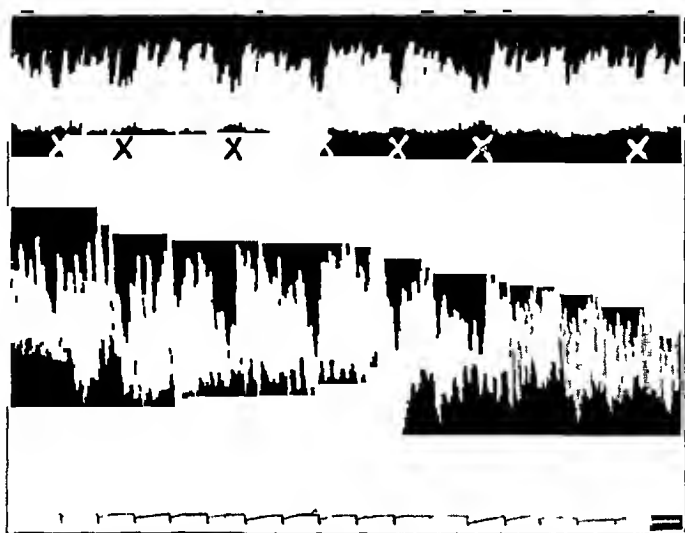


Fig 3—Record of gastric motility (middle tracing) during digestion of first protein meal after twenty-four days of protein restriction—beginning thirty-five minutes after ingestion of 225 Gm of roast veal. Upper tracing is a respiratory record with unusually persistent intermittent increases in rate (X, X, X) synchronous with hunger sensations, lower tracing, time in minutes.

the breathing accordingly. This, however, required distinct effort and a close attention to detail, neither of which was noticeably involved in the natural manifestation. On the other hand, it was more difficult to breathe normally (at a slow rate) when a strong sensation occurred than it was to imitate the rapid breathing. Difficulty in preventing the increase in the respiratory rate might therefore, in a measure, serve as a check test. Another question investigated was whether the respiratory increase would be manifested during sleep. The necessary experimentation proved difficult, but such results as seemed dependable warranted the conclusion that the respiratory rate was not affected during sound sleep, and that respiratory irregularities might be taken as an index of light or dreamy sleep or of a transition between sleep and wakefulness.

Before F H more permanently discontinued the protein restriction which was necessary to prevent the hunger sensation with the respiratory increase from disappearing, attempts were made to determine in what particular respects this sensation could be distinguished subjectively from the ordinary hunger sensation which has little if any effect on the respiratory rate. Serious difficulties were encountered here, first, because a hunger sensation of the type which when strong gave rise to objective evidence of an increase in the respiratory rate, did not yield such evidence when the sensation was mild or of brief duration, second, because the hunger sensation with the change in the respiratory rate was frequently synchronous with the gastric contractions, and third, because some gastric contractions (of F H as well as of another subject) were recorded which did not cause any sensation. The complexity of the situation easily explains why it has not been possible to discover the hunger sensation with the increase in the respiratory rate by subjective experience alone. Nevertheless, repeated observation, with the assistance of objective methods and under wide variations in conditions, made it certain that the hunger sensation with the respiratory reflex differs from the ordinary hunger sensation more in a qualitative than in a quantitative way. Besides being more diffuse or more irradiating, the hunger sensation with the change in the respiratory rate was less sharply defined in its onset and abatement than the ordinary hunger sensation which is referred more or less directly to the gastric contractions. In this respect, it was somewhat similar to sensation accompanying increases in gastric tonus. At the onset of sensation, this similarity usually gave the impression that a strong gastric contraction was about to take place, but neither contraction nor tonus increase necessarily followed. A sensation caused by tonus variations alone was always milder and less diffuse than the hunger sensation with the respiratory increase. Besides this, the ordinary hunger sensation often impressed F H as being simply a reminder of a state of emptiness which could be remedied by ingesting some nonnutritive material, while the hunger sensation with the respiratory reflex appeared to be a more direct call for nourishing food. It might be described as a famishing sensation or as hunger with a keen appetite. However, it should be emphasized that the two sensations had a common element in that both involved a desire to ingest "something," and it is evidently this common element, rather than the peculiarities of the individual sensations, that forces itself most on consciousness.

#### THE RÔLE OF GASTRIC ACIDITY IN THE HUNGER COMPLEX

Boring<sup>3</sup> reported that the introduction of 5 or 10 per cent hydrochloric acid into the stomach produced a sensation of hunger. Carlson<sup>2</sup>

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3 Boring, E. G. *Am J Psychol* **26** 1, 1915

using 0.5 per cent hydrochloric acid, found that it gave rise to an appetite-like sensation. A relation between gastric acidity and the intensity of the desire to eat was also noted by one of us in connection with previous studies (Hoelzel<sup>4</sup>). This relationship was observed to hold for variations in the gastric acidity which occurred naturally (before prolonged fasting was undertaken) as well as for artificial modifications. The artificial changes were made by adding a small amount of a strong solution of hydrochloric acid or sodium hydroxide to the aspirated gastric residuum and then returning it to the stomach. In these tests, the acidity was always kept within natural limits (0 to 0.5 per cent free hydrochloric acid), and the volume of the residuum remained practically unchanged, because a little was used for titration before and after the hydrochloric acid or sodium hydroxide was added. It could not be settled by these more or less preliminary tests whether hunger or appetite was modified.

The relation between the gastric acidity and the intensity of the desire to eat observed before was obscured during prolonged fasting and during the first four months after fasting. The desire to eat was then often as keen with the acidity relatively low as it had been previously with high acidity. Nevertheless, when considered separately, the effect of variations in gastric acidity was also indicated in certain ways during this period. Thus, with the acidity relatively higher, the desire to eat was more intense during the last half of the thirty-three day fast than during the last half of the subsequent forty-one day fast. During the first four months after fasting, it was also noticed that the amount of protein which was relished or which could be tolerated depended largely on the available hydrochloric acid secretion (Hoelzel<sup>4</sup>). The effect of gastric acidity on the general desire to eat was, however, complicated during this period by at least one other factor, namely, increased gastrointestinal sensibility, this will be discussed more fully in the next section.

It will be recalled that the hunger sensation with the increase in the respiratory rate was observed for the first time during the latter part of the forty-one day fast. The average gastric acidity was then relatively low. During the first four months after the fast, this sensation was observed with both high and low acidity. On the basis of this experience alone, a relationship between this hunger sensation and gastric acidity was not indicated. However, as suggested in the foregoing, the relationship may have been obscured during this period because of increased sensibility and other factors. That this was the case became evident later when the prefasting state of nutrition and more normal sensibility had apparently been restored. Then the hunger sensation with the respiratory reflex disappeared and remained absent for about two months, during which the average or potential gastric acidity was kept

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4 Hoelzel, F. *Am J Physiol* **73** 463, 1925, *ibid* **77** 166 1926

low with a moderately high protein intake, and it again returned with protein restriction which increased the acidity. We have already mentioned that the return of the hunger sensation with the change in the respiratory rate at this time showed that this sensation had always developed with protein starvation, as the acidity was incidentally increased with the protein restriction, it also became evident that this hunger sensation was the basis of the increased desire to eat which had previously been attributed to the higher acidity. Later, the relationship between gastric acidity and the hunger sensation with the increase in the respiratory rate was also demonstrated during digestion as the sensation developed most clearly with the first protein meal after a period of protein restriction—that is, at a time when the digestive acidity would be expected to be highest (fig 3).

This observed relationship between gastric acidity, the peculiar hunger sensation and the increase in the respiratory rate was tested further. First, the spontaneous or natural appearance of the sensation was suppressed by lowering the potential gastric acidity with a high protein intake. Then, after the gastric residuum was removed, from 10 to 25 cc of 0.5 per cent hydrochloric acid was introduced into the stomach (by tube) to determine whether the acid would cause the hunger sensation. Water was used for control. A brief sensation usually developed within from one to four minutes after the introduction of the acid, and the sensation generally recurred a few times before the effect of the acid had disappeared entirely. By that time the acidity was also considerably reduced. With the repeated introduction of fresh acid, the effect gradually became less pronounced or was obscured by the development of a mild continuous burning sensation which, however, did not materially affect the rate of respiration. Moreover, the effect of the acid became more vague as time elapsed after the spontaneous appearance of the sensation had been suppressed. Water did not cause the peculiar hunger sensation. Two tenths per cent hydrochloric acid yielded inconclusive results. On one occasion, a sensory response occurred immediately or while the (0.5 per cent) acid was still being introduced. The tip of the tube, in this instance, was thought to have been drawn well into the antrum by gastric motility.

The foregoing observations and the fact that the hunger sensation was often preceded by an increase in gastric tonus or contraction seemed to indicate that the acid became effective on passing into the duodenum. Accordingly, a number of tests were made by introducing about 10 cc of 0.5 per cent hydrochloric acid, by tube, directly into the duodenum and again using water for control. In these tests, the position of the tube was determined mainly by the character of the aspirate. The subject (F. H.) was unaware as to whether hydrochloric acid or water was introduced as the observer (N. K.) selected and introduced the test fluids in neg-

ulal oidei and with adequate time intervals between the individual tests. A sensory response was not always elicited by the hydrochloric acid. This might have been caused by neutralization of the acid or by failure to reach a specific site or sufficient area in which the acid might have been effective. The sensation was not manifested clearly more than once after any given injection, and then the latent period was usually shorter than when acid was introduced into the stomach. Most of the tests were made with the tube kept in one position—with the tip apparently from 5 to 15 cm. beyond the pylorus (as inferred by the length of the tubing swallowed). In one test, however, the tube was permitted to pass well into the duodenum, and then acid was introduced at various intervals while the tube was being gradually drawn back. When the tube was well in, the results were not uniform. When the tip of the tube appeared to have been at the pylorus, an immediate sensory response to the acid occurred. When the tube was pulled back a little farther, the aspirate showed that the tip was back in the stomach.

The relative consistency of the results with hydrochloric acid was, however, upset by the observation that water introduced into the duodenum, also gave rise, at times, to the hunger sensation with an increase in the respiratory rate. This was unexpected, and led to the previously mentioned tests concerning the effect of anticipating the involved hunger sensation. Anticipation may have intensified some of the respiratory changes, but deliberate attempts to avoid increases in the respiratory rate indicated more definitely that water sometimes gave rise to the hunger sensation with the respiratory reflex or to a sensation which could not be distinguished from it. This does not mean that when water enters the duodenum normally by way of the stomach it can elicit the sensation. Natural conditions are not simulated when substances are introduced directly into the duodenum. The presence of even the tube alone introduces an abnormal factor. The first time that the tube was introduced, the subject felt some nausea and dizziness. The second time only dizziness was occasioned. After that, no sensation could be attributed directly to the presence of the tube alone, but its presence added to the introduction of water, regardless of whether or not the duodenum was at the moment naturally prepared to receive anything, may have given rise to sensation which would not occur normally. Nevertheless, evidence was obtained, without the use of the duodenal tube, that other substances besides hydrochloric acid might also elicit the hunger sensation with the increase in the respiratory rate. For instance, during a period of protein restriction, this sensation was manifested clearly while test meals made up chiefly of fat (butter) were being digested. Did the fat or fatty acid elicit the sensation, or did sufficient hydrochloric acid occasionally accumulate and give rise to the sensation even though a number of aspirated digestive fractions showed practically no free

acid? However, as the hunger sensation with the increase in the respiratory rate did not develop with similar fat meals after protein realimentation, altered sensibility may have played the major rôle in determining results.

In this connection, another observation is of interest. As mentioned in the foregoing, some nausea was occasioned by the presence of the tube in the duodenum for the first time. It was therefore thought that close observation might reveal a sensation as the tube passed through

TABLE 1—*Showing Duodenal Regurgitation More Directly Increased with Protein Restriction than with Increased Gastric Acidity*

Date (1925)	Number of Aspirations§	Average per Cent Free Hydrochloric Acid	Approximate per Cent Bile Contamination*	Preceding Regimen†
Oct 5	7	0.050	15	After liberal diet with about 36 Kg meat
6	6	0.055	40	After liberal diet with about 30 Kg meat
7	6	0.075	65	After liberal diet with about 27 Kg meat
8	6	0.022	35	After liberal diet with about 36 Kg meat
9	5	0.002	20	After liberal diet with about 27 Kg meat
10	6	0.023	50	After liberal diet with about 18 Kg meat
11	3	0.006	50	After liberal diet with about 18 Kg meat
12	5	0.026	80	After liberal diet with about 09 Kg meat
13	5	0.040	60	After liberal diet with about 09 Kg meat
14	4	0.010	10	After liberal diet with about 18 Kg meat
15	5	0.112	40	After liberal diet with protein restriction
16	4	0.090	85	After 2 days of protein restriction
17	6	0.073	75	After 3 days of protein restriction
18	4	0.065	90	After 4 days of protein restriction
19	6	0.108	85	After 5 days of protein restriction
20	5	0.096	80	After 6 days of protein restriction
21	10	0.113	75	After modified fast day about 100 calories
22	7	0.087	30	After liberal diet with 42 egg whites
23	9	0.094	55	After liberal diet with 36 egg whites
24	8	0.103	0	After liberal diet with 48 egg whites
25	6	0.135	85	After modified fast day about 50 calories
26	6	0.060	0	After diet with 48 egg yolks
27	10	0.053	10	After diet with 48 egg yolks
28	8	0.065	100	After day of fasting
29	6	0.090	0	After 4,950 calories including 38 egg whites
30	7	0.103	15	After 2,500 calories including 29 egg whites
31	7	0.064	15	After 2,500 calories including 29 egg whites
Nov 1	6	0.105	85	After day of fasting
2	8	0.089	35	After 2,700 calories including 6 eggs
3	7	0.080	85	After 2,400 calories with protein restriction

§ These gastric aspirations were made at thirty minute intervals early in the day (before eating or drinking).

\* In calculating the percentage of bile contamination, a moderately strong bile tinge in each aspirate was regarded as 100 per cent contamination. Faint traces and unusual amounts of bile were allowed for accordingly.

† The earlier part of the period in this table is not strictly comparable to the latter part because of the difference in proximity to and influence of, the prolonged fasting which ended September 13 and to which sixteen days of protein restriction were added.

the pylorus. Hence, in waiting for the tube to pass on one occasion, test aspirations were made whenever a sensation occurred. It was thus found that a sensation which was believed to be accompanied by the respiratory reflex developed twice as duodenal contents were regurgitated into the stomach. This observation suggested that the hunger sensation resulting from high acidity as well as that resulting from fat in the stomach might have been due to motility involved in the increased duodenal regurgitation which acid and fat are known to occasion. Moreover, the fact that regurgitation is increased during fasting (Boldy-

ieff,<sup>5</sup> Carlson,<sup>6</sup> Hoelzel<sup>4</sup>), and the fact that it remained somewhat marked during the first four months after fasting, further supported the hypothesis that the hunger sensation with the respiratory increase was associated with regurgitation. In addition to this, a relation between protein starvation and increased regurgitation was suggested by data like those submitted in table 1. Here protein restriction was apparently a more direct cause of regurgitation than increased gastric acidity. Further observation, however, failed to substantiate consistently this otherwise interesting observation, perhaps because such violent contrasts in the protein intake did not occur again. Conclusive evidence also could not be obtained in support of the possibility that the hunger sensation with the change in the respiratory rate was associated only with duodenal regurgitation.

Summing up the evidence, it appears certain that the acid (and perhaps peptic activity) of the gastric secretion, by acting in the duodenum and mainly near the pylorus, was a factor in eliciting the hunger sensation with the respiratory increase. Whether the acid determined the sensation directly, or whether it gave rise to a pyloric or duodenal spasm or to some other form of motor activity which in turn elicited the sensation, is an unsettled question. The hunger sensation with the change in the respiratory rate was probably the hunger sensation which Boing found had occurred after the introduction of hydrochloric acid into the stomach. This sensation was probably also the "keen appetite" which, as Pawlow<sup>7</sup> observed, had developed after taking a little wine at a time when the desire to eat was not spontaneous. Moreover, the "appetite-like" sensation noted by Carlson after the administration of hydrochloric acid or of other fluids, which might have acted either directly or after stimulating the acid secretion, may have been a mild form of the hunger sensation with the increase in the respiratory rate—too mild to yield distinct objective evidence of such an increase. Besides this, the claim of Boldyreff<sup>8</sup> that the periodic gastric contractions do not give rise to hunger may be explainable by his further claim that the stomach is alkaline at such times, in contrast to this, American observers find more or less acid and hunger sensation. The lack of hunger in tuberculous subjects, in spite of essentially normal hunger contractions (Meyer<sup>9</sup>), may also be explainable by the low gastric acidity which is commonly found in patients with tuberculosis.

In this connection, it is interesting to note that Carlson found human gastric juice containing from 0.45 to 0.5 per cent hydrochloric acid effective in giving rise to sensation, but not that containing 0.2 per

5 Boldyreff, W. *Ergebn d. Physiol.* **11** 121, 1911.

6 Carlson, A. J. *Am. J. Physiol.* **45** 120, 1918.

7 Pawlow, I. P. *The Work of the Digestive Glands*, London, 1910.

8 Boldyreff, W. *Quart. J. Exper. Physiol.* **10** 175, 1916.

9 Meyer, J. *Physiology of Stomach*, *Arch. Int. Med.* **22** 759 (Dec.) 1918.

cent (Carlson and Braafladt<sup>10</sup>) Baird, Campbell and Hern<sup>11</sup> concluded that the duodenum is insensitive to twentieth normal or 0.2 per cent hydrochloric acid. Barsony and Egan,<sup>12</sup> using from 0.2 to 0.36 per cent hydrochloric acid and introducing from 3 to 15 cc into the duodenum, observed that the smaller quantities and weaker acid had practically no effect, while the larger quantities and stronger acid nearly always gave rise to disagreeable sensations, nausea or dizziness, which, however, shortly disappeared. They also noted variations in the responses in different subjects. Wichert and Dworjetz<sup>13</sup> state that 10 cc of tenth normal hydrochloric acid introduced into the duodenum gave rise to a disagreeable sensation or nausea unless the juice had been warmed. In tests made on two other subjects in our study, the repeated introduction of 25 cc of 0.5 per cent hydrochloric acid into the stomach gave rise to a mild burning sensation which one of these subjects reported as involving an increased desire to eat. An increase in the respiratory rate, however, did not develop. It is common knowledge that hydrochloric acid frequently has a similar effect in cases of gastric achylia. Limiting ourselves to observations on man, these observations compare favorably with each other, as well as with the observations on F. H., particularly, if allowance is made for variations in the degree of sensibility.<sup>14</sup>

#### SOME OBSERVATIONS ON THE SENSIBILITY OF THE DIGESTIVE TRACT

It was pointed out in the preceding section that the hunger sensation with the increase in the respiratory rate was sometimes manifested when the acidity was relatively low after fasting as well as during fasting. Hence, if it is granted that ordinarily a relatively high gastric acidity is required to give rise to the sensation, some other factor must have favored the development of the sensation when the acidity was relatively low. This factor appears to have been increased sensibility. If it is not conceded that the gastric acidity played any rôle in eliciting the sensation, a consideration of the conditions again seems to compel us to assume increased sensibility to account for the sensation.

However, besides being a necessary assumption to explain the occurrence of the hunger sensation with the respiratory reflex, an increased sensibility of the digestive tract during fasting, protein stasis

10 Carlson, A. J., and Braafladt, L. H. *Am J Physiol* **36** 153, 1914

11 Baird, M. McC., Campbell, J. M. H., and Hern, J. R. B. *Guy's Hosp Rep* **74** 23, 1924

12 Barsony, T., and Egan, E. *Munchen med Wchnschr* **72** 1242, 1925

13 Wichert, M., and Dworjetz, W. *Arch f Verdaungskr* **34** 158, 1925

14 Since this article was written the work of Palmer, which corroborates our observations in a number of ways, has been published. Palmer, W. L. *The Mechanism of Pain in Gastric and in Duodenal Ulcers*, *Arch Int Med* **38** 603 (Nov.) 1926, **38** 694 (Dec.) 1926, **39** 109 (Jan.) 1927

tion and undernutrition was indicated by other observations. For instance, in connection with the study of the basal metabolism made by one of us (N. K.<sup>1</sup>), an attempt was made to insure uniform conditions in the digestive tract by having the subject (F. H.) ingest a quantity of nonnutritive bulky material shortly before determinations on the metabolism were made. Instead of guaranteeing gastric motor quiescence, however, as was to be expected from Carlson's<sup>2</sup> observations, periods of what appeared to be gastric hunger contractions were not inhibited, were prolonged or were actually initiated by the ingestion of this material (about 50 Gm of cellulose flour soaked in petroleum jelly and taken with 50 cc of water flavored with saccharin). The contractions (as recorded with the balloon method) sometimes appeared as early as three minutes after the ingestion of the mixture, which always gave rise to a sense of fullness. They usually continued until all the ingested material left, or was forced out of, the stomach—from one-half to one hour—and were generally felt as more or less gradually increasing hunger sensations. This was repeatedly observed during the period of about four months after the prolonged fasting, when the hunger sensation with the increase in the respiratory rate was manifested both with high and low gastric acidity. Later, however, the same quantity of nonnutritive material stopped the hunger contractions and occasionally remained in the stomach as long as three hours. This could only mean that the sensibility to mechanical stimuli had been increased on the previous occasions.

The experimentation necessary to yield similar objective data to show a hypersensibility to mechanical stimuli during prolonged fasting was not undertaken. However, because of subjective experience during previous fasts (Carlson,<sup>6</sup> Kunde<sup>15</sup>), F. H. restricted the use of non-nutritive bulk and even of water somewhat during the last two prolonged fasts (Hoelzel<sup>4</sup>). Bulk was used only during the latter part of the fasts and chiefly to promote forward peristalsis, as, after the third or fourth day of fasting, it was never possible to suppress the hunger sensations satisfactorily with nonnutritive material alone, regardless of how much was ingested. This does not mean that the ingestion of inert substances did not give rise to a sense of fullness, in fact, the sense of fullness usually developed quickly. This appeared to be due, at least in part, to an increase in gastric tonus which made it difficult to ingest large quantities, but which was also the prelude to a period of gastric contractions. Presumably, in certain pathologic states, similar motor responses of a hypersensitive stomach limit the amount of food which can be ingested with comfort, and may even give rise to painful sensation.

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15 Kunde, M. M. *J. Metab. Research* 3:399, 1923.

Some observations also indicated that the mere presence of a balloon in the stomach, to record gastric motility, increased the motility somewhat during fasting and undernutrition. Comparison with subjective experience alone and with the data obtained by the aspiration method (Hoelzel<sup>4</sup>) pointed to this. Nevertheless, all methods of observation indicated a definite increase in motility during fasting and undernutrition. This raises the question whether the secretions in the hypersensitive digestive tract serve as the stimulus which gives rise to the increased motility. This would be practically certain if the accumulating secretions or excretions were an adequate, or normal stimulus of gastric motility as for instance, Anitschkow<sup>16</sup> apparently would have us believe. But the work of Bulatao and Carlson<sup>17</sup> suggests that the blood sugar level is an important factor in determining gastric motility. Besides this, there is often gastric hypermotility in true achlorhydria. Without further data, we are therefore not in a position to decide whether the secretions should be accorded a material rôle.

The following instances may be cited as further evidence of an increased sensibility of the digestive tract resulting from fasting and undernutrition. 1. Carlson<sup>18</sup> found that smoking tended to produce nausea after a few days of fasting. He also refers to other evidence of a hypersensitive state. 2. Rutimeyer,<sup>19</sup> reporting the experience of a professional fasting woman, stated that she found it necessary to restrict the use of spices for some time after fasting. 3. The regrettable developments after the thirty-one day fast of Levanzin (Benedict<sup>20</sup>) were probably due to the use of food (lemons, etc.) which was irritating to a hypersensitive digestive tract. 4. On the twelfth day of a twenty-six day fast of F. H., nausea and burning sensations were occasioned as a result of swallowing a little gravel, such an effect was not noted when larger quantities of similar material were ingested under more normal circumstances. 5. F. H. found that he had made a mistake in breaking this twenty-six day fast with unsweetened (although highly diluted) lemonade. Excruciating burning and gnawing sensations developed and recurred periodically for twenty-four hours. Water gave no relief. Tomatoes aggravated the sensations. They disappeared after potatoes, fried with an excessive amount of fat, were eaten. 6. The only time that nausea was experienced during the thirty-three day fast of F. H. was after drinking some warm water on the thirty-second day, warm water did not have such an effect at other times. 7. Considerable violence was done when a salad of green pepper was used on the fifth day after the forty-one day fast of F. H. The subject had hardly ever eaten green

16 Anitschkow, S. W. *Ztschr. f. d. ges. exper. Med.* **42** 405, 1924.

17 Bulatao, E., and Carlson, A. J. *Am. J. Physiol.* **69** 107, 1924.

18 Carlson, A. J. *Am. J. Physiol.* **33** 95, 1914 (Footnote 2).

19 Rutimeyer, L. *Centralbl. f. innere Med.* **30** 233, 1909.

20 Benedict, F. G. *A Study of Prolonged Fasting*, Washington, 1915.

pepper before, but it was tried at this time in a practically futile attempt to find something which would help to satisfy while the protein intake was being restricted for experimental purposes. The pepper, smothered in olive oil, was not observed to be particularly irritating to the taste, although it certainly was not bland. F. H. slept a few hours immediately after finishing the salad, and woke to find that his mouth and the rest of the digestive tract seemed to be "on fire." The burning sensation did not disappear entirely until about three days later, the blandest foods that suggested themselves being used in the meantime. This experience is hard to explain. Did it take several hours for a mild irritation of the mucous membrane of the mouth to become effective, by the gradual development of an inflammation, or did the pepper become effective mainly after absorption from the intestine, and give rise to a form of allergy? Whatever the explanation, this experience seemed to show decisively that there is a specific type of increased visceral sensibility. 8 In addition to the foregoing, candy and jam caused a burning sensation in the mouth, involving the tongue and gums, and in the throat when used to break a fast. This burning developed immediately on contact and usually disappeared within ten or fifteen minutes. It was not elicited again by the further ingestion of sweets. 9 Ice cream was always too cold to be relished for some time after fasting as well as during prolonged undernutrition. It was repeatedly felt to be so cold that its sweetness could not be tasted. Its coldness was felt practically all the way down the esophagus, this sensation disappearing at about the level of the cardia. 10 A specific type of sensibility was manifested during modified protein starvation thus. F. H. had frequently used celery in the normal diet without noting any unusual effect. After a few days of protein restriction, the juice of celery (taken to insure vitamin and salt balance) always gave rise to extreme dizziness or to a sinking sensation. This seemed to be a form of nausea without a feeling of disgust toward food. Other vegetable juices did not have such an effect. Celery alone or salted did not appeal to the taste during these periods, but it was particularly appreciated when mixed with other food. The effect, however, was always the same and independent of the manner in which it was taken. 11 The increased intestinal rate or improved bowel condition after fasting (Hoelzel,<sup>21</sup> Kunde<sup>15</sup>) is probably due to increased gastro-intestinal sensibility. 12 The exquisite taste of foods for some time after prolonged fasting may also only reflect increased sensibility.

These observations leave little room for doubt that the sensibility of the alimentary canal is increased as a consequence of fasting or undernutrition. That this hypersensibility is physiologic must be admitted,

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21 Hoelzel, F. The Rate of Progress of Food Residues Through the Bowel (privately published paper), 1924

since realimentation always brings about more normal conditions. If it is granted that the increased sensibility is physiologic, what is its nature?

If conditions in the mouth and upper part of the esophagus are considered first, it will hardly be doubted that the increased sensibility is in the mucosa or other superficial structures. Such an explanation of increased sensibility in the lower part of the esophagus might, however, be questioned. Ryle,<sup>22</sup> for instance, leaves the impression that he regards heartburn as chiefly being due to contractions or spasms in the cardiac region. In support of this view, he cites Hurst's<sup>23</sup> observation that the esophagus is insensitive to hydrochloric acid. However, if the acid of the gastric contents gives rise to heartburn, it probably does so only after prolonged or repeated contact with the esophageal mucosa. Hurst's<sup>23</sup> report does not contain any evidence that he duplicated the probable conditions. These were closely simulated in the application of the method used by one of us (F. H. \*) in securing data regarding the acidity and volume of the contents of the "empty" or fasting stomach. The aspirations were then made by first lowering the tube well into the stomach and then applying suction intermittently while the tube was gradually drawn back into the esophagus. The tube was always lowered a second time and occasionally a third time to repeat the process before an aspiration was considered complete, and the tube was withdrawn entirely. These aspirations were usually made at intervals of half an hour and were sometimes repeated from ten to thirty-two times in one day. It was originally intended to avoid swallowing saliva throughout the periods of observation, but it soon became evident that this was impracticable. The reason was that the acid adhering to the tube and being repeatedly brought into the esophagus gave rise to a burning sensation, apparently heartburn. Consequently the swallowing of saliva was generally completely avoided only during actual intubation. A burning sensation developed most rapidly when the gastric acidity was relatively high, but heartburn was also distinctly experienced (during digestion) when the acidity was relatively low, at that time, gastric regurgitation occurred frequently. This evidently occasioned a more or less continuous irritation of the esophagus by the gastric contents and led to heartburn in spite of the relatively low acidity. The gastric regurgitation probably occasioned concomitant variations in pressure or contractions in the esophagus, such as Payne and Poulton<sup>24</sup> found associated with heartburn. There is no evidence, however, that such contractions alone could give rise to a burning sensation.

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22 Ryle, J. A. *Gastric Function in Health and Disease*, London, 1926.

23 Hurst, A. F. *The Sensibility of the Alimentary Canal*, London, 1911.

24 Payne, W. W., and Poulton, E. P. *Quart. J. Med.* **17**: 53, 1923.

This, however, does not mean that the sensation in heartburn comes from the mucosa. If the intact esophageal mucosa gave rise to sensation, the sensory response to acid might well be expected to be immediate. But as the burning sensations in the experience of F. H. developed gradually, and as (slight) bleeding at the cardia was eventually and repeatedly occasioned when aspirations were continued after pain began (Hoelzel<sup>1</sup>), the sensation evidently came from the submucosal structures, possibly as a result of the irritation of afferent fibers accompanying the blood vessels. Breslau<sup>25</sup>, Kappis,<sup>26</sup> Propping<sup>27</sup> and Ritter,<sup>28</sup> among others who studied visceral sensibility, concluded that sensory nerves accompany the larger blood vessels. However, the work of Odermatt<sup>29</sup> indicates that sensory nerves also accompany or surround the capillaries, and that they respond chiefly to chemical stimuli, especially, when such stimuli are applied under pressure. Odermatt's observations therefore make it seem possible that adequate chemical stimuli, particularly when assisted by pressure caused by increased tonus or contractions, may elicit sensation anywhere in the digestive tract provided the mucosa is penetrated.

Besides suggesting the nature of the sensibility involved in heartburn, the experience of F. H., principally when bleeding was produced at the cardia, emphasized the difficulty of localizing the exact site of some types of visceral sensation by subjective analysis alone. It was clear at first that some burning came from the esophagus as the sensation was rather high. However, by swallowing a little saliva after each aspiration, irritation by acid at a high level was prevented. When the gastric acidity was greater than usual, it was impossible to prevent the development of pain at lower levels, the stomach then appeared to become raw when the aspiration periods were prolonged. It was some time before it was noticed that the pain was always particularly sharp (sometimes like a toothache) when suction was applied while the tip of the tube was at the level of the cardia. It is not likely that there was any specially sensitive spot lower down in the stomach, and yet the entire stomach appeared to be raw. In view of this, it is easy to understand that similar sensation elicited at other circumscribed sites, either in or somewhat beyond the stomach, may also be sufficiently diffuse to be referred to the gastric region in a general way. Nevertheless, as Ryle's<sup>30</sup> and our own observations indicate, sensations which are apparently caused by contractions alone are usually more definitely localized.

25 Breslau, F. Beitr. z. klin. Chir. **121** 301, 1921

26 Kappis, M. Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26** 493, 1913

27 Propping. Beitr. z. klin. Chir. **63** 690, 1909

28 Ritter, C. Zentralbl. f. Chir. **35** 609, 1908, Arch. f. klin. Chir. **90** 389, 1909

29 Odermatt, W. Beitr. z. klin. Chir. **127** 1, 1922

30 Ryle, J. A. Lancet **1** 895, 1926

If we next consider gastric sensibility on the assumption that sensation due to chemical stimuli comes mainly by way of afferent fibers in the submucosa or by way of perivascular nerves, it follows that such stimuli cannot reach these fibers easily since the normal gastric (fundal) mucosa is practically impermeable to most substances. Alcohol is an exception and likewise is said to give rise to sensation from the stomach (Carlson,<sup>2</sup> Hurst<sup>23</sup>). However, with an injured, inflamed or ulcerated mucosa, conditions would be altered. Claims, like that of Hurst, that even the ulcerated gastric mucosa is insensitive to hydrochloric acid can be met by counter-claims. Thus, Palmer, working at the Cook County Hospital, found the sensibility to hydrochloric acid sufficiently uniform to use it (hydrochloric acid introduced into the stomach) as a test for the presence, or proof of the cure, of an ulcer (personal communication<sup>14</sup>). Sensation from an injured gastric mucosa was probably involved on one occasion when increasingly painful and practically continuous burning and gnawing sensations were experienced by F. H. after the ingestion of seventeen lemons. As the eating of the lemons made the tongue and gums bleed (thus making it too painful to ingest more), the gastric mucosa was probably also affected. The painful gnawing was evidently partly due to the digestive contractions. The eating of fat brought relief.

The opinion was previously held by one of us (F. H.) that the normal gastric mucosa possessed a degree of tactile sensibility. This view seemed necessary to explain an element in hunger sensation which did not appear to be referable to contractions of the musculaxis alone. Accordingly, some tests were made during one period by swallowing a quantity of barely moistened knotted string or millet seed after first removing the gastric residuum. These substances were swallowed thus because it was not possible to force them through an aspiration tube in the dry state. However, instead of the expected hunger or hunger-like sensations (which arose in a few preliminary tests when the gastric residuum was not first removed), thirst developed. This thirst again disappeared within about thirty minutes without drinking. It apparently lasted until sufficient gastric juice was secreted to soak thoroughly the barely moist material which had been swallowed. This perhaps means that there is a gastric (or duodenal) component in thirst. The sensation involved here seemed to be a vague or dull burning referable to the epigastric region rather than a sense of dryness referable to the pharynx. An intestinal component in thirst was believed previously to be indicated by the observation that thirst, which would again disappear without drinking, often developed with diarrhea. Gastro-intestinal conditions may also explain the thirst or sense of dryness which cannot be relieved by drinking, and which was observed during fasting by Kunde<sup>15</sup> and in some fasts by F. H.

The problem of gastric sensibility is complicated by the fact that most test substances introduced into the stomach pass into the duodenum and may give rise to sensation there. Without check tests on the duodenum, it is not certain that a sensation has actually come from the stomach. Granting, however, that it comes from the stomach, this does not tell us whether the sensation comes from the stomach as a whole or only from a circumscribed site. London,<sup>31</sup> for instance, presents evidence that the sensation of fullness comes from the cardia. The observations of Rogers and Martin<sup>32</sup> suggest that the gastric contractions may give rise to hunger sensation from a position near the pylorus. In fact, it seems probable that the hunger sensation comes from this region rather than from the fundus, because the contractions close to the pylorus are stronger than those in the fundus (Moritz<sup>33</sup>), and because the functional rôle of the antrum in gastric physiology is such that it appears to be a more probable site of sensibility than the fundus.

Chemical stimuli would be more likely to cause sensation in the duodenum (and in the gastric antrum) than in the fundus of the stomach, for the increased power of absorption here is evidence of a more permeable mucosa. This does not exclude the possibility or the practical certainty that contractions of the duodenum are also involved in, or may independently give rise to, sensation—apparently, with antiperistalsis, contributing to the sensation of nausea (Alvarez,<sup>34</sup> Fitzgibbon,<sup>35</sup> Ivy and Vloedman,<sup>36</sup> Keeton<sup>37</sup> and Wheelon<sup>38</sup>). But as motility usually involves a shifting of the contents of the digestive tract, peristaltic activity may bring acid gastric contents into the duodenum, and, as evidence presented in the preceding section indicates, under some conditions, the acid may give rise to a more intense hunger sensation than some gastric hunger contractions. On the other hand, nausea, headache, dizziness, some weakness and so-called symptoms of auto-intoxication are probably often the result of the irritation of the sensitive duodenum by contents which have been brought from a lower level of the digestive tract, or which remain stagnating in the duodenum.

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31 London, E. S. *Experimentelle Physiologie und Pathologie der Verdauung*, Berlin, 1925.

32 Rogers, F. T., and Martin, C. L. *Am J Physiol* **76** 349, 1926.

33 Moritz, F. *Ztschr f Biol* **32** 313, 1895.

34 Alvarez, W. C. Reverse Peristalsis in the Bowel, A Precursor of Vomiting, *J A M A* **85** 1051 (Oct 3) 1925.

35 Fitzgibbon, J. H. Reverse Peristalsis Associated with Nausea, *J A M A* **85** 1889 (Dec 12) 1925.

36 Ivy, A. C., and Vloedman, D. A. *Am J Physiol* **72** 99, 1925.

37 Keeton, R. W. Nausea and Related Sensations Elicited by Duodenal Stimulation, *Arch Int Med* **35** 687 (June) 1925.

38 Wheelon, H. Symptoms Associated with Duodenal Retention and Reverse Motility, *J A M A* **86** 326 (Jan 30) 1926.

However, whether hunger sensation and nausea are more directly referable to motor activity or to chemical stimulation, it is significant that the duodenum apparently contributes to both sensations. Nausea is often thought of as the direct antithesis of hunger, but both are related to food intake—hunger being a craving for, and nausea a feeling against, the ingestion of food, while a conception of satiety as the neutral point between hunger and nausea might be defended. The fact that some people are nauseated when hungry, or that they cannot distinguish clearly between the sensations (Boring<sup>3</sup>) indicates an element of similarity. One of us (N. K.) has personally experienced this confusion from time to time, while F. H. has often found that symptoms of autointoxication (dopiness, weakness and mild headache) either cleared up or decreased considerably with periods of hunger contractions which normally involved a predominance of powerful forward peristalsis. The simultaneous manifestation of nausea, satiety and hunger (or appetite) also seems easily demonstrable. For instance, whenever F. H. attempted to satisfy hunger with a diet restricted to fat, the feeling that enough had been ingested (satiety regarding fat) soon developed. A keen desire to eat (other food) might persist, but nausea would develop when attempts were made to satisfy this desire by the ingestion of more fat. Proteins or carbohydrates would be eaten with avidity on such occasions. An excessive fat intake evidently provokes nausea by increasing antiperistalsis, as suggested by the duodenal regurgitation which fat is known to excite. The blending of nausea and the hunger sensation makes it appear that there is an overlapping of the sites of origin of the two sensations, or that both come from the same site but are elicited by different stimuli. This site seems to be the parapyloic region (gastric antrum, pylorus and first part of the duodenum). Whether the sensations are caused by motility, by chemical stimuli or by both, the variety of motor and chemical activity in this region could account for every kind and degree of sensation related to food—including idiosyncrasies and the unusual cravings often associated with pregnancy (the cause of which is suggested by hyperemesis gravidarum).

After what has been said, little need be added concerning the probable immediate cause of the increased sensibility of the digestive tract induced by fasting and undernutrition. The development of edema as a result of protein deficiency (Kohman<sup>39</sup>) after fasting (Hoelzel,<sup>14</sup> Kunde<sup>40</sup>) or with malnutrition (Jackson,<sup>41</sup> Morgulis<sup>42</sup>) shows that a more or less generalized increased permeability is involved in each case.

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39 Kohman, E. *Am J Physiol* **51** 378, 1920.

40 Kunde, M. M. *Edema*, *Arch Int Med* **38** 57 (July 15) 1926.

41 Jackson, C. M. *The Effects of Inanition and Malnutrition upon Growth and Structure*, Philadelphia, 1925.

42 Morgulis, S. *Fasting and Undernutrition*, New York, 1923.

This would account for the increased sensibility to chemical stimuli in the digestive tract and incidentally might explain the increased gastric acidity (after fasting or protein starvation) which, in turn, appears to be a powerful stimulus of sensation

#### THE PROBLEM OF SPECIFIC HUNGER SENSATION

Evvard<sup>43</sup> found that hogs were able to select their food instinctively better than nutrition experts could choose it for them. Mitchell and Mendel<sup>44</sup> observed that rats and mice could, to a large extent, discriminate between adequate and inadequate diets. Rubner<sup>45</sup> pointed out that various races of mankind instinctively use diets with a total calory intake well adjusted to needs and with a protein ratio which is strikingly uniform, although the sources of the food elements vary widely. This seems to indicate that normally some fundamental physiologic factors impel animals and man to take fairly adequate quantities of the various food elements. That is, the foregoing observations suggest that the general urge to eat is a complex—the sum of a number of simpler urges or specific hunger drives. Such a view of hunger at least appears worthy of consideration.

Thirst is apparently a type of specific hunger. The young mammal or the human infant, normally receiving milk to satisfy both hunger and thirst, can hardly be aware of thirst as distinct from hunger. The probability is that it is usually a little thirsty when it is hungry, and generally a little hungry whenever it is thirsty. All that such a young animal can become aware of is that it wants to suckle, or that it wants "more"—more milk. Mature animals, including man, would hardly become more aware of a distinct sense of thirst than a fish if the diet always contained enough or more than enough water. In support of such a view, it is of interest to find a psychologist like McDougall<sup>46</sup> saying that mild sensations of hunger and thirst seem alike. To distinguish, he takes a drink of water. If that satisfies, he was thirsty, if not, he was hungry! F. H. has met with similar confusion. During some periods he used large quantities of fresh fruit in a salt-free diet. The diet, consequently, contained more than enough water to prevent thirst under ordinary conditions. Sometimes three or four months would pass without an occasion arising which would call for a drink. When hot weather set in after such a period, additional water was occasionally called for, but thirst was not recognized immediately. What was noticed then was a sense of discomfort or a hunger-like sensation involving a desire for "something," but accompanied by the

43 Evvard, J. M. *Proc. Iowa Acad. Sc.* **22** 375, 1915.

44 Mitchell, H. S., and Mendel, L. B. *Am. J. Physiol.* **58** 211, 1921.

45 Rubner, M. *Deutsche med. Wchnschr.* **51** 259, 1925.

46 McDougall, W. *Outline of Psychology*, New York, 1923.

feeling that food would not be relished. Some might call it hunger without appetite (for the usual food). Generally, the fact that thirst was being experienced dawned on the mind when the subject came in contact with water (as in washing the hands). After the distinction between hunger and thirst was thus revived, it became easy to discriminate again later. A gastro-intestinal factor in thirst, such as has already been referred to, might be the source of possible confusion, or serve as a link, between thirst sensation and hunger in general. At any rate, these considerations seem to make it logical to regard thirst as a specific type of hunger—water hunger—as Durrig<sup>47</sup> considers it.

As the foregoing indicates, we apparently come to distinguish between thirst and ordinary hunger (the desire for the other food elements) mainly because sharp contrasts are often brought about, and because a specific element (water) free from gross admixture with other elements exists and is frequently used to satisfy this particular craving independently. This points to the way in which we can determine experimentally whether ordinary hunger is not a complex made up of simpler urges, such as, protein hunger, carbohydrate hunger, salt hunger and vitamin or other types of hunger. It was with this conception in mind that an experimental search for evidence of a protein hunger sensation (because of the vital importance of protein) was begun by one of us (Hoelzel<sup>48</sup>). The assumption was that if a protein hunger sensation exists, observations made while the protein intake was sufficiently varied should give evidence of such a sensation. The first observation was that the gastric acidity is raised by protein restriction and is again lowered by protein realimentation (Hoelzel<sup>48</sup>). This observation was partly accidental, as it was more or less incidental to an investigation of the relation of gastric acidity to hunger in general (Hoelzel<sup>48</sup>). It was also observed that, as a consequence of modified protein starvation, peculiarly persistent hunger sensations developed which could be dispelled only by protein realimentation. As indicated in a preceding section, it then became clear that this hunger involved the sensation which strikingly increased the respiratory rate. Therefore, the conclusion seems warranted that the hunger sensation with the increase in the respiratory rate is an index of protein hunger just as pharyngeal dryness (Cannon<sup>49</sup>) or esophageal contractions (Muller<sup>49</sup>) and a possible gastric or intestinal factor (F. H.) indicate thirst. To say that the sensation with the respiratory reflex is an index of protein appetite, instead of protein hunger, would be to ignore important facts and fundamentals. In the first place, the sensation gives no direct indication that protein is desired. That is discovered by trial and error.

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47 Durrig, A. *Appetit*, Vienna, 1925.

48 Cannon, W. B. *Proc. Roy. Soc. Lond. Ser. B*, **90** 283, 1918.

49 Muller, L. R. *Deutsche med. Wchnschr.* **46** 113, 1920.

Moreover, prolonged protein restriction appears to decrease protein appetite, that is, it tends to make one forget the taste of protein food just as prolonged fasting may make one indifferent to customary foods. Besides this, a sensation which is strong enough to "take the breath away" is as logically referred to as hunger as the ordinary hunger sensation which has little, if any, effect on respiration.

The question may well be raised here whether the ordinary hunger sensation, which is more or less directly associated with the gastric motor activity, is in any sense an index of a specific need. A number of observations make it highly probable that the ordinary hunger sensation most directly reflects the carbohydrate need. In support of this there is, in the first place, the observation of Bulatao and Carlson<sup>50</sup> that the hunger contractions can be influenced strikingly by the blood sugar level. About the same time, Harris<sup>50</sup> reported the observation of hypoglycemia in patients who became hungry or weak soon after a meal. Luckhardt's<sup>51</sup> earlier observation of abnormally strong hunger contractions in diabetes also pointed to a relation between carbohydrate metabolism and the gastric contractions. Obviously, it is not the blood sugar level but the utilizable sugar that counts. The common experience that sweets before a meal may quickly dissipate hunger is perhaps to be explained mainly by the effect of the carbohydrate on gastrointestinal motility or tonus. An earlier practice of F. H. in beginning a fast might also be mentioned here. This was to eat nothing but sweets on the day before fasting. It was then possible to abstain from food with ease for at least one day. An excess in the use of sweets evidently also accounts for the frequent lack of "appetite" after parties or holidays.

In view of considerations like the foregoing, some observations were made with the balloon method of study to determine the specific effect of variations in the carbohydrate intake while the protein intake was adequate and fairly constant. It was thus found that, while a period of gastric hunger contractions did not develop during as long a time as six hours following the emptying of the stomach after a high carbohydrate intake, with complete carbohydrate restriction, periodic motor activity was manifested even during digestion, that is, after the ingestion of a meal of fat (fig 4). However, it was not possible to lengthen progressively the time between the periodic gastric contractions by a prolonged high carbohydrate intake. In fact, the periods again became more frequent under such circumstances. On the other hand, with a continued high fat intake, the intervals between the periods became longer after an initial shortening. The explanation may be that a

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<sup>50</sup> Harris, S. Hyperinsulinism and Dysinsulinism, *J. A. M. A.* **83** 729 (Sept. 6) 1924.

<sup>51</sup> Luckhardt, A. B. *Am. J. Physiol.* **33** 313, 1914.

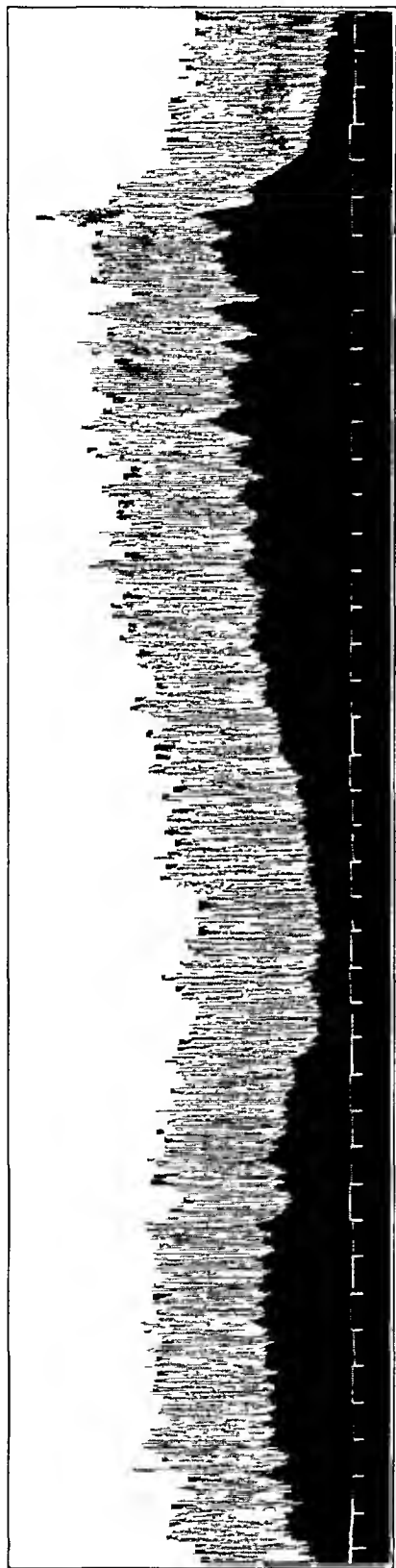


Fig 4.—Periodic element in gastric motor activity during digestion of meal of fat (115 Gm butter), time in minutes given below

habitual high carbohydrate intake leads to a quicker response in the glycogenic function, as suggested by Bock and others<sup>52</sup> This would tend to nullify the effect of the carbohydrate excess which would otherwise depress motility A continued high fat intake leads to a rise in blood sugar (Weeks and others<sup>53</sup>) which perhaps counteracts the initial effect of this type of dietary excess and again lengthens the intervals between the periodic contractions In other words, an adaptation to the use of excessive quantities of fat or carbohydrate may take place The effects of variations in the carbohydrate and fat intakes are therefore obscured in prolonged experiments, but seem clear in briefer tests

The aforementioned observation of periodic motility during the digestion of meals of fat is of particular interest It seems possible to explain this occurrence as follows Periodic motility is probably an autonomic function of the digestive tract This, however, can be modified considerably by variation in the blood sugar level or utilizable carbohydrate By the ingestion of meals containing carbohydrate (or protein which serves as source of carbohydrate), the periodic element in motility may be suppressed by the absorbed carbohydrate, which cannot occur when the meals contain an excess of fat or fat only Nevertheless, variations in glycogenesis or in pancreatic (insulin) secretion also appear likely to modify the results This deduction is made from the observations of Harris as well as from our own observation of a period of increased motility which developed on one occasion during the digestion of a carbohydrate meal and once after the ingestion of a protein meal, before the stomach had been emptied This periodic motility was usually experienced as mild hunger In fact, the subjective experience of hunger shortly after the ingestion of meals of fat led to the investigation That this periodic digestive motility is not a peculiarity of the subject (F H) is shown by the independent finding, by Mulinos,<sup>54</sup> of a similar phenomenon in dogs Carman<sup>55</sup> also stated that, contrary to the teaching of Cannon<sup>56</sup> and others, he sometimes observed (with the roentgen ray) that a period of gastric motor activity at the beginning of digestion was followed by a brief period of relative or complete inactivity Some irregularities in digestive motility should therefore be regarded as normal Naturally, it is more difficult to discover such fluctuations in motor activity with the limitations of the

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52 Bock, J C, Schneider, H, and Gilbert, M J Biol Chem **69** 9, 1926

53 Weeks, D F, Renner, D S, Allen, F M, and Wishart, M B J Metab Research **3** 317, 1923

54 Mulinos, M G Am J Physiol **77** 158, 1926

55 Carman, R D The Roentgen Diagnosis of Diseases of the Alimentary Canal, Philadelphia, 1921

56 Cannon, W B The Mechanical Factors of Digestion, New York, 1911

roentgen-ray method of study than with the more continuous record obtainable by the balloon method

The changes in the gastric hunger contractions observed during prolonged fasting also seem to be largely explainable by the alteration in the carbohydrate metabolism as reflected by variations in the blood sugar level. The determinations for blood sugar, as shown in table 2, were made during the thirty-three day fast of F. H., by Dr. Larson of the University of Illinois College of Medicine by courtesy of Prof. Welker's arrangement.

These figures show that the blood sugar decreased at the beginning of fasting and remained at a low level throughout. It did not decrease continuously. Likewise, gastric motility increased over the prefasting motility, but it apparently did not continue to increase after the first few days (fig. 5). Irregular variations in the frequency and intensity of the hunger periods were noted; likewise, the blood sugar level varied. A

TABLE 2—*The Determinations for Blood Sugar During the Thirty-Three Day Fast*

Date (1925)		Per Cent
May 28	First day of fast	0.087
June 1	Fifth day of fast	0.058
5	Ninth day of fast	0.043
9	Thirteenth day of fast	0.067
16	Twentieth day of fast	0.069
22	Twenty-fourth day of fast	0.058
July 1	Four hours after breaking fast*	0.094
7	Before eating, six days after fast	0.104

\* The carbon dioxide combining power of the blood (determined by Dr. Kunde) was 39 before, and 52 four hours after, breaking the fast.

closer relationship could not be claimed without more data. The variations suggest that considerable changes may occur within a few hours. There is also a suggestion that the blood sugar level paralleled the curve of gastric acidity (Hoelzel<sup>4</sup>) in increasing after an initial decrease. Lennox<sup>57</sup> recently reported the observation of similar variations in the blood sugar level during fasting.

The foregoing observations make it highly probable that the gastric hunger contractions more or less directly reflect the carbohydrate need. However, in view of the relation of the carbohydrate reserve in man to the nutritive state in general, carbohydrate hunger probably also indicates the total caloric need. Ordinary hunger, as Harris has suggested, may therefore primarily be a desire for glucose. Hence, the gastric hunger contractions apparently serve simultaneously to give rise to a specific and also to a nonspecific hunger sensation. The nonspecific element is obviously emphasized, because the general desire to eat is somewhat intimately related to the degree of emptiness of the stomach.

<sup>57</sup> Lennox, W. G., O'Connor, M., and Bellinger, M. Chemical Changes in the Blood During Fasting in the Human Subject, *Arch. Int. Med.* **38**: 553 (Nov.) 1926.

Besides thirst, protein hunger and carbohydrate hunger, there are a number of manifestations of specific hunger which future investigation may prove to involve characteristic peripheral sensation complexes, although they may also be of central origin. Among these is the well known salt hunger of some herbivores. The seeming lure of the water of certain springs for some invalids, especially when benefit is obtained, probably also indicates a specific salt hunger. The osteophagia of cattle is a well investigated type of specific hunger. To refer to it as a perverted appetite (Green<sup>58</sup>), when it reflects a physiologic need for phosphorus, is obviously illogical. It would seem more consistent to say that cattle that do not eat bones, when they are available, and when phosphorus is deficient in the natural food supply, have a perverted appetite (more correctly, perhaps, a perverted hunger). Durig<sup>47</sup> refers to the fat hunger experienced in the central empires during the war, and may be

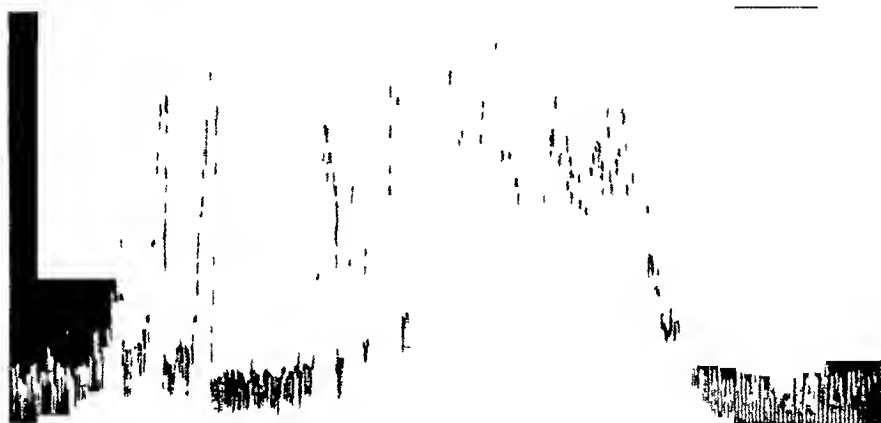


Fig 5—Period of gastric hunger contractions of F. H. on fortieth day of fasting, total time, twenty minutes

right in suggesting that this probably involved a call for vitamins. Vitamin hunger seems to be the explanation of the following experience. Before F. H. had any knowledge of vitamin A, it was observed that, after using only olive oil as food for a few days, butter mixed with sugar tasted better than anything else, with the possible exception of ice cream. Why the ingestion of one fat food (olive oil) should lead to a particular liking for another fat food (butter or cream) was not explainable until a few years later when the fat-soluble vitamin A became known. The exclusive use of olive oil apparently created a vitamin A hunger. The particular craving for sugar in this experience is understandable when the rôle of carbohydrate in ordinary fat metabolism is borne in mind. In this connection, it seems significant that it has not been possible to find a specific sensation complex which might be an index of a need of fat. Perhaps fat and carbohydrate, being more or less

<sup>58</sup> Green, H. H. *Physiol Rev* 5 336, 1925

physiologic substitutes for one another, are craved in much the same way—by sensation mainly referable to gastric motility

However, aside from the evidence of specific hunger which has been given, the observations in vitamin deficiency studies suggest that specific hunger sensation is an inevitable consequence of specific starvation. As is well known now, the deficiency of essential food elements usually gives rise to characteristic symptom complexes in which the digestive tract is generally involved (McCarrison,<sup>59</sup> Cowgill and others<sup>60</sup>). When not carried to pathologic extremes, the symptoms can be remedied by supplying the proper food. The repeated alleviation of specific symptoms, whatever their nature or however mild, by the ingestion of particular food elements would naturally lead to such symptoms being regarded as the index of hunger for the corresponding elements. Such a relationship and association between the unpleasant gastric sensations and the food intake in general Carlson<sup>12</sup> believed explained the reference of hunger to the stomach, nothing further has been proved to explain the relation of thirst to specific sensations which are said to indicate it.

According to the foregoing, hunger viewed as a special instinct would normally serve as a guide in nutrition, but it is commonly believed that often this is not true. Without more precise experimental data, we can here only suggest the factors which may account for the apparent exceptions. First, a normal manifestation of hunger demands the normal functioning of the physiologic mechanism involved. Abnormalities may occur in this mechanism just as they occur elsewhere. Second, granting a normal hunger mechanism, the development of a normal (conscious) use of this mechanism (appetite) obviously depends on the use of adequate food while the psychic relationships between hunger and food intake (taste-memory processes) are becoming more or less fixed. It is also perhaps not always borne in mind that hunger does not tell us what to eat, it serves primarily to impel us to try things. Whether man will even try those foods which would yield the most fundamental or most complete degree of satisfaction depends largely on environmental, cultural and educational factors. Third, there is a quantitative factor in hunger whereby the elements of which the largest amounts are needed (carbohydrate, fat and protein) become most prominent. The habitual relative overuse of such elements may therefore tend to develop naturally. Fourth, with a surplus of food, such as commonly obtains among mankind, the tendency is to reject food which is less agreeable with respect to texture and taste. Hence, green-stuffs which are often not only coarse textured, but which may con-

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59 McCarrison, R. *Studies in Deficiency Diseases*, London, 1921.

60 Cowgill, G. R., Deuel, H. J., Jr., Plummer, N., and Messer, F. C. *Am J Physiol* **77** 389, 1926.

tain distasteful or even toxic ingredients (tannin, etc.) will naturally be used sparingly, especially when a fair degree of satisfaction is yielded by the liberal use of slightly deficient but otherwise more agreeable food. If, however, a sufficiently acute hunger for essential food elements is created by prolonged fasting or specific starvation, foods (such as greens) which may otherwise be regarded as disagreeable are likely to be relished far more than foods (such as sweets) which are ordinarily preferred. This has been a common experience of F. H. Taste or appetite therefore may not be a safe guide in nutrition, but appetite is not hunger ("instinct").

#### COMMENT

Much of the foregoing is based on observations made on only one subject. Obviously, similar studies on other subjects would be desirable and would have been made if the necessary subjects had been available. In fact, some of the experimentation with F. H. was not carried further because it was felt that the fundamental observations should be confirmed on others. The protein hunger sensation was not observed during the fifteen day fast of F. H. studied by Carlson,<sup>6</sup> but evidence of it may have escaped notice. The published records of gastric motility during that fast are not clear enough to give definite evidence, and the unpublished graphs were unfortunately destroyed after having been saved for four years. A consideration of all the factors involved also gives the impression that the sensation may develop sooner with simple but rigid protein restriction than with complete fasting. Aside from this, the possibility that others may be affected differently from F. H. cannot be entirely disregarded, on the other hand, it does not seem likely that anything so fundamental would vary much in different persons. In this connection, it should perhaps also be emphasized that the protein hunger sensation continued to be manifested for four months after fasting only because of the experimental dieting of that period. With a continued adequate protein intake immediately after the forty-one day fast, the sensation probably would have disappeared within three weeks.

A weak point in our study is involved in the fact that respiration can be affected by conscious attention with relative ease. Reasons were given which indicate that our results cannot be thus explained away. Nevertheless, it has since been thought that it might have been better to observe the heart rate, assuming that it is affected by the protein hunger sensation. Electrocardiograms during such hunger might also reveal something of interest. One taken during digestion, a few days after the thirty-three day fast, showed nothing in spite of marked edema (Kunde<sup>40</sup>). The heart, however, is probably affected in some way by prolonged restriction of protein. Transient sensations, as if one would collapse unless proper food were taken, were noted from time to

time by F H, and were thought to be due to circulatory disturbances. The suspicion arises that it was some such sensation, rather than alarm over a low excretion of nitrogen, which terminated the rigid protein restriction experiment reported by Smith<sup>61</sup>. A subject who knew nothing about the excretion of nitrogen would probably have felt as much "alarmed" and might have stopped just as soon or sooner.

#### SUMMARY

Evidence of a specific type of hunger sensation, which gave rise to a striking increase in the respiratory rate, has been obtained (in one subject). This sensation was somewhat independent of the periodic gastric hunger contractions. Under extreme conditions, it was manifested even with food in the stomach. It differed from the ordinary hunger sensation mainly in being more diffuse or more radiating.

This peculiar hunger sensation appeared to be elicited chiefly by the action of the gastric contents in a hypersensitive duodenum. Increased sensibility, however, was a more important factor than gastric acidity. Evidence is given which indicates that fasting, protein starvation or undernutrition may give rise to a hypersensitive state in the digestive tract.

As the hunger sensation with the increase in the respiratory rate developed repeatedly in consequence of protein starvation (including fasting in this category), and as it could easily be suppressed by protein realimentation, this sensation is believed to be an index of protein hunger. The gastric hunger contractions and tonus variations are shown to reflect the carbohydrate need to a large extent. A gastro-intestinal component in thirst, which would tend to link thirst with hunger sensation, was also believed to be found.

These observations and other considerations are thought to support the view that the general complex of hunger sensation is comprised of a number of simpler specific urges or conditions which normally impel a fairly adequate intake of the various food elements. However, in contrast to hunger, taste or appetite may not be safe guides in nutrition.

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61 Smith, M. J. Biol. Chem. **68** 15, 1926

# SEVERE CHRONIC GLOMERULAR NEPHRITIS

WITHOUT HYPERTENSION CARDIAC HYPERTROPHY OR RETINAL  
CHANGES REPORT OF TWO CASES \*

EDWIN G BANNICK MD

ROCHESTER MINN

For many years medical teaching has emphasized the association of hypertension cardiac hypertrophy and retinal changes in the severe cases of chronic glomerular nephritis. These observations have been so reliable in most cases especially in those with marked retention of nitrogen that physicians have learned to rely on them as valuable aids in differential diagnosis and to regard one or more of these three observations as almost necessary for a correct diagnosis of chronic glomerular nephritis with uremia. Rare exceptions to this general rule however have long been recognized. In 1905 Müller<sup>1</sup> mentioned the association of tuberculosis acute sepsis, typhoid fever and ascending renal infections with some cases of chronic diffuse nephritis in which elevation of blood pressure or cardiac hypertrophy did not occur. In certain of these cases the greater part of the kidney was destroyed but true uremia was rare.

In 1908 Jores<sup>2</sup> showed that the degree of destruction of tissue in the kidney could not be the decisive causative factor of cardiac hypertrophy or elevation of blood pressure. He found typical examples of granular atrophy of the kidneys in which both the arterial tension and the size of the heart were normal.

In 1922 Foster<sup>3</sup> described two cases in which nephritis had developed in early life and in which death had occurred before the twentieth year. The blood pressure had been normal throughout the disease. At necropsy the kidneys were smaller than normal and granular. Sections showed the ordinary picture of chronic glomerular nephritis. More recently French writers<sup>4</sup> have reported 'chronic nephritis with azotemia and without arterial hypertension' but although their cases were some-

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\* From The Mayo Foundation

1 Müller Friedrich Morbus Brightii Verhandl d deutsch Gesellsch f Chir 7-9 64, 1905

2 Jores, Leonard Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie von pathologische-anatomischen Standpunkt Deutsches Arch f klin Med 94.1 1908

3 Foster N B The Relations of Hypertension to Cardiorenal Diseases Am J M Sc 164 808 1922

4 Bouchut L, and Ravault, P Les nephritis chroniques azotemiques Presse med 1.67, 1926 Laroche Guy and Desmouliere A Les nephritis chroniques urémigènes Presse med 2 689 1924

what similar to, they did not seem to coincide entirely with, the group under discussion

Although these unusual cases have been recognized and some of them reported, there is great need of more clinical data in order to study and appreciate better the relationship of hypertension and cardiac hypertrophy to nephritis, a point emphasized by Foster and others. It is for this purpose that the following cases are reported

In case 1 the records are complete and permit conclusions to be drawn which are definite enough to give title to this article. In the second case the data are not so complete, and all of the blood pressure readings not so definitely normal as in case 1, but the two cases are similar and so unusual that it seems advisable to report both

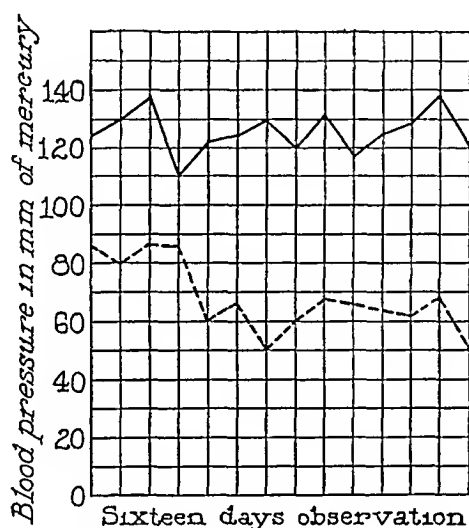


Fig 1—Blood pressure readings in case 1. Note that systolic pressures higher than 140 and diastolic pressures higher than 90 were not observed. The continuous line indicates systolic pressure, the broken line, diastolic pressure.

CASE 1—A man, aged 49, was admitted to the Clinic on Feb 25, 1926, complaining of weakness and vomiting. He had been a gold miner for the past seven years. Following influenza in 1919, he had noticed a slightly productive cough and some loss of weight for several months, but he had gradually recovered. About Dec 1, 1925, he contracted a cold. This was followed by malaise, slight anorexia and some loss of weight and strength. However, he continued to work until early in February, when he became profoundly weak and began to vomit soon after eating. Because of the persistent vomiting and loss in weight of more than 20 pounds (9 Kg) cancer was suspected, and he was referred to the Clinic.

The patient showed clinical evidence of uremia with associated weakness, dehydration and moderate anemia and was admitted to the hospital immediately. Although the blood contained 304 mg of urea and 15.6 mg of creatinine for each 100 cc, the blood pressure was only 124 systolic and 86 diastolic. The eye-grounds appeared normal except for slight anemia, there were no signs of cardiac hypertrophy or decompensation, and there was little peripheral sclerosis. The hemoglobin content (Dare) was 36 per cent, the erythrocytes numbered 2,540,000, and the leukocytes 7,000. The urine showed a specific gravity of

1014, albumin 1, and many red blood cells. The plasma sodium chloride was 495 mg for each 100 cc, the carbon dioxide combining power of the plasma was 64 per cent, but other observations were not suggestive of high intestinal toxemia, and gastric retention was not present.

The patient improved somewhat for about ten days, when he contracted acute parotitis, followed by otitis media, mastoiditis, cellulitis of the face and bronchitis, he died from uremia on March 12, sixteen days after admission. The blood urea had risen to 346 mg, creatinine to 17 mg and plasma phosphates to 83 mg, but the blood pressure had remained normal, the highest recorded pressure being 138 systolic and 85 diastolic (fig 1). Edema had not been present, and there were not any signs of cardiac collapse until the last day of the illness. The clinical diagnosis was chronic glomerular nephritis with the terminal conditions mentioned.

The observations at necropsy were as follows: (1) chronic glomerular nephritis, (2) adhesive pericarditis, (3) acute bronchitis, with edema and

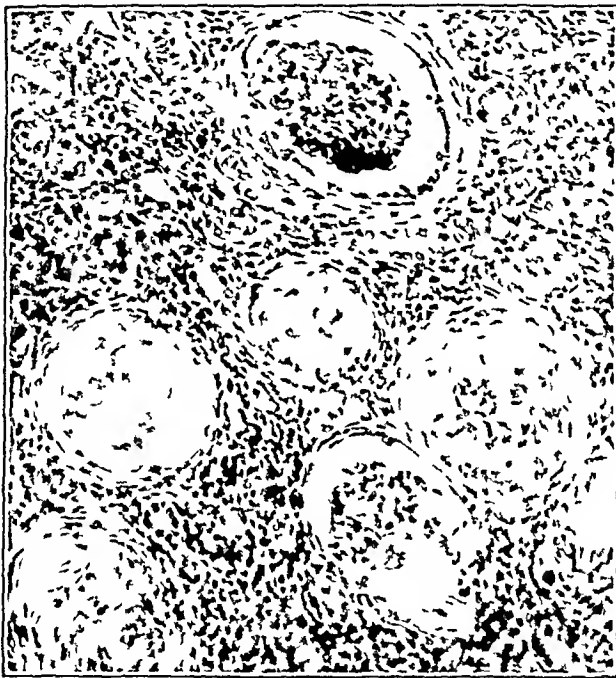


Fig 2—Section from kidney showing marked glomerular injury,  $\times 140$

congestion of the lungs and small pulmonary abscesses, (4) cellulitis of the face, parotitis, otitis media and mastoiditis, (5) old hyperplastic tuberculosis of the hilum lymph nodes, (6) adenomas of the suprarenals, (7) adenomas of the right lobe of the prostate, (8) slightly enlarged spleen (weight 320 Gm), and (9) diverticula of the urinary bladder with trabeculation of the wall. The changes of chief interest in view of the clinical course were in the kidneys, heart and blood vessels.

The left kidney weighed 102 Gm. Its capsule was slightly adherent, and when stripped, left a granular surface. The remnants of fetal lobulations were fairly well marked, and numerous small petechial hemorrhagic areas were seen beneath the surface. Cut sections showed a thinned cortex with many petechial hemorrhagic areas throughout the pale tissue. There was a small cystic area in the lower pole measuring 5 by 3 mm and filled with yellowish, gelatinous, translucent material. The right kidney weighed 120 Gm and showed more prominence of fetal lobulations. There was a turkey-egg mottling due to areas of petechial hemorrhage in the cortex and small, yellow, firm, raised nodules. On

section, the cortex was thinned and the markings indistinct as in the left kidney. Abnormalities were not noted in either the pelvis or the ureter in either kidney.

Microscopic examination of the kidneys showed extensive chronic glomerular nephritis with secondary involvement of the tubules and marked interstitial changes (figs 2 and 3). Most of the glomeruli were either partially or completely obliterated. Some were hyalinized; some hemorrhagic and some showed lobulation and crescent formations. Bowman's capsules were markedly thickened. The tubules were distended and some contained albuminous material. Extensive diffuse fibrosis was present throughout.

The pericardium was thickened and tightly adherent throughout. Edema of the fatty portion of the epicardium was present. The heart with some of the adherent pericardium weighed 340 Gm, and the true weight of the heart was estimated at a little over 300 Gm. The myocardium was pale brown. The mural endocardium and valves did not present notable lesions. The foramen



Fig 3—Section from kidney showing diffuseness of renal injury and the absence of sclerosis of renal vessels,  $\times 60$ . See necropsy records.

ovale was closed, and the base of the aorta showed little if any sclerosis. The coronary vessels were of normal caliber and showed practically no sclerosis. The following measurements were made: aortic valve, 6.5 cm; mitral valve, 10 cm; tricuspid valve, 13 cm; pulmonary valve, 6 cm; depth of left ventricle, 7.5 cm; thickness of left ventricle, 1.4 cm; depth of right ventricle, 9 cm; and thickness of right ventricle, 0.3 cm.

On microscopic examination of the heart, the cells were found apparently normal in size and staining characteristics. The nuclei were regular and fairly even in size and shape. There was a slight increase in the amount of fibrous tissue, particularly in the proximity of the blood vessels, and in these situations a small collection of lymphocytes and a slight perivascular infiltration. The endocardium was slightly thickened. There was no fatty degeneration.

Very little arteriosclerosis was present. In the vessels examined, the intima and media were of almost normal thickness and arteriosclerosis was graded 1— One of the renal vessels is shown in fig 3.

CASE 2—A boy, aged 15, came to the Mayo Clinic on Jan 7, 1925, because of an abscess of the right axilla, anorexia, weakness and malaise. He had had scarlet fever at the age of 9, influenza at 10, tonsillitis at 12, and furunculosis at 13. One month before admission to the Clinic, he had felt malaise and weakness and had stopped going to school. A week later, his throat became sore and the cervical lymph nodes enlarged. In a few days, a painful, tender lump was noted beneath the right arm. This mass was incised and drainage established, but the patient gradually became weaker and drowsier.

The patient appeared stuporous and anemic, and the breath had a uremic odor. Edema was not present, the blood pressure was 112 systolic and 70 diastolic, and a retinal examination did not reveal anything abnormal with the exception of slight anemia. The heart was not hypertrophied and seemed normal, the urine showed a specific gravity of 1.009 with much albumin and occasional pus cells. The blood urea was 158 mg and creatinine 6 mg for each 100 cc. The phenolsulphonphthalein test showed only a faint return of the dye in two hours. The hemoglobin content (Dare) was 57 per cent, the erythrocytes numbered 2,900,000 and the leukocytes 23,300. The abscess in the right axilla was still draining pus, but apparently the drainage was not free, so another incision was required. The local condition improved rapidly.

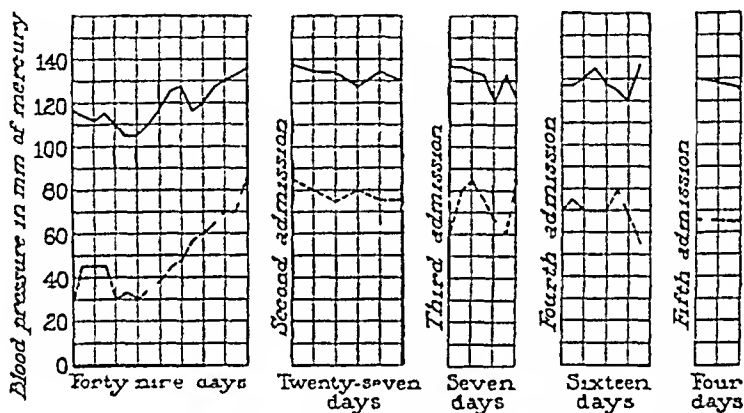


Fig 4—Blood pressure readings in case 2 during the entire period of observation. Note that systolic pressures higher than 140, and diastolic pressures higher than 90 were not observed. Note high pulse pressures. The continuous line indicates systolic pressure, the broken line, diastolic pressure.

following this, but the patient gradually became more toxic and manifested severe acidosis. The blood urea reached 220 mg, the creatinine 17.2 mg, and the carbon dioxide combining power of the plasma dropped to 15 per cent. However, under intensive treatment the patient improved remarkably and was dismissed from observation on Feb 25, 1925. The blood urea at that time was 53 mg and the creatinine 4 mg, the urine showed only traces of albumin, and the blood count was practically normal.

During the entire period in the hospital, the blood pressure was recorded nearly every day, and the highest systolic pressure was 138 and the highest diastolic pressure 88. The pulse pressure was higher than normal most of the time, especially during the first few weeks when the patient was acutely ill (fig 4). The eyegrounds remained normal.

The patient was readmitted to the hospital on May 12, 1925. He was feeling well and looked strong and healthy, but there was evidence of renal insufficiency with a low specific gravity of the urine, albumin 2. The blood urea was 75 mg and creatinine 5.5 mg. Fundal and cardiac observations were negative. The systolic blood pressure was 138 and the diastolic 88, which was the highest pressure recorded during the twenty-seven days that the patient was in the hospital.

The patient was dismissed improved. He returned again on July 22, 1925. He seemed to be well and strong, and the only changes observed since the last examination were that the blood urea content had risen to 127 mg and the creatinine to 5.6 mg. The highest recorded blood pressure was 138 systolic and 60 diastolic. The pulse pressure was again somewhat increased.

When again admitted, Sept. 10, 1925, he seemed to have fared considerably. Anemia was marked. Blood urea was 134 mg and creatinine 5.2 mg. The whole picture was classical for asthenic uremia, except that as before, the fundi seemed normal, the blood pressure was 128 systolic and 70 diastolic and evidence of cardiac hypertrophy or weakness was not present. During sixteen days in the hospital, the highest recorded systolic pressure was 138, at which time the diastolic pressure was 66. The highest pulse pressure was 72.

Finally the patient came back on March 19, 1926, in terminal uremia with severe anemia and acidosis. The blood urea was 459 mg and creatinine 19.6 mg. Hemoglobin content (Dare) was 30 per cent, the erythrocytes numbered 1,490,000, and the carbon dioxide combining power of the plasma was 20 per cent. There still were not any retinal changes nor any evidence of cardiac hypertrophy. The systolic pressure was 130 and the diastolic 65. The patient wished to return home. He died there ten days later. Postmortem examination was not performed.

#### COMMENT

Case 1 presented considerable difficulty in diagnosis when the patient was admitted to the hospital. Because of the normal fundi, cardiac condition and the blood pressure, together with the high blood urea content, moderate lowering of the plasma sodium chloride, slight tendency toward alkalosis and a questionable history of malignant neoplasm, high intestinal toxemia with associated renal insufficiency was at first suspected. The absence of gastric retention, however, the rapid drop of the carbon dioxide combining power of the plasma, the extremely high blood creatinine and the results of urinalysis pointed to primary nephritis. The insidious onset and slow development without edema indicated chronic glomerular nephritis rather than an acute or subacute type, and this diagnosis was definitely confirmed at necropsy. Chronic pyelonephritis had been carefully considered, but the history and observations made this possibility unlikely.

In case 2 the blood pressure readings were slightly higher than normal on a few occasions for a boy, aged 15 or 16, but these observations were infrequent, most of the many blood pressure readings recorded during fourteen months of intermittent observation being within normal limits. On many occasions the blood pressure during the early part of this patient's first admission was decidedly below normal, which was probably due to sepsis with acidosis and exhaustion, but these factors had no bearing on later examinations when the patient seemed to be strong and well. He had been working on the farm prior to his second and third admissions, and had returned on these occasions because he had been requested to do so. The pulse pressure, however, was considerably increased during his first admission. This may also have been associated with his exhaustion, since it was less pronounced on subsequent examinations.

## CONCLUSION

Rare cases of severe chronic glomerular nephritis terminating in uremia may occur without hypertension, cardiac hypertrophy or retinal changes. The appreciation of this possibility aids in the correct diagnosis of these unusual cases and adds important data to the study of hypertension and nephritis.

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## CORRECTION

In the article by Drs. Edward H. Mason and Howard H. Mason, "Effect of Ultraviolet Light on Oxygen Consumption and on Total Metabolism" (*ARCH. INT. MED.* 39:317 [March] 1927), the summary of blood counts on page 327 should follow the data concerning case six, rather than those concerning case three.

## Book Reviews

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**TRANSFUSION OF BLOOD** By HENRY M FEINBLATT, M D, Assistant Clinical Professor of Medicine, The Long Island College Hospital, Brooklyn, N Y, Hematologist to the United Israel-Zion Hospital, Pathologist to St Peter's Hospital, Assistant Attending Physician to the King's County Hospital, Hematologist to the Shore Road Hospital Cloth pp 137, with 24 illustrations New York The Macmillan Company, 1926

This book is an excellent and careful critical survey of the subject of blood transfusion as it stands today The early chapters give a complete historical resume of the steps in the development of blood transfusion, with particular reference to physiologic considerations

A concise and clear description of blood groupings, donors, indications for transfusion and the dangers resulting from transfusion is considered in separate chapters

One wishes that the author had devoted more time and space to a discussion of the various methods of transfusion, especially considering the citrate methods His own method is given in great detail and might lead the reader to believe that this method is the one of choice, instead of being one of the direct methods

The final chapters are short and concise and are devoted to blood transfusion in children and autotransfusion In the chapter on blood transfusion in children, consideration is given to the body weight in calculating the average amount given for a single transfusion The author states that it is rarely necessary to utilize the superior longitudinal sinus, as one is seldom unable to pierce a child's vein by properly cutting down on it Full details of both procedures, however, are given Intraperitoneal transfusion is fully discussed in both the direct and citrate methods and, therefore, furnishes an additional means of performing blood transfusions under conditions in which the veins are so small and collapsed as to be entirely inaccessible

Great care has been taken in carefully going over and sorting out the literature, and an extensive bibliography of both foreign and American contributions is included, based largely on the author's personal experience and views

**KIDNEY DISEASE FROM THE PHYSICIAN'S POINT OF VIEW** By ROLFE FLOYD, M D, Junior Attending Physician and Pathologist at the Roosevelt Hospital Cloth Price, \$2.50 Pp 181 New York Dougherty

In the preface to this book, it is stated that its purpose is to bring together in short compass, information which the medical practitioner needs for an intelligent understanding of kidney disease—it is largely a statement of the work of others Its contribution consists in the attempt to gather and digest as much information as possible, and to present it in concise, intelligible and usable form Careful study of the book convinces one that the author has spent much effort, has kept to the object set forth in the preface and has done well However well informed one may be concerning kidney disease, he could hardly fail to profit by a study of the material presented here, and the author's keenly critical and analytic discussion of it

The classifications of nephritis, with reasons and lack of reasons involved, are well presented The works of Delafield and of Volhard and Fahr are considered at length A fairly severe criticism of "nephrosis" as an additional class of kidney disease is well supported by the author's analysis of the information available concerning this subject

Excretion of salt and its disturbances constitute an interesting and instructive chapter. To those not entirely familiar with the value of chemical studies of the urine and blood in persons with nephritis, this is especially recommended. There is, of necessity, overlapping of subjects when chemical studies bring in discussions of edema, dropsy, uremia and hypertension, but these are all handled with the clearness that could come only from one who has the known facts concerning them well in hand.

Remembering the object of this book, and even considering how rapidly books become out of date, it is a pleasure to recommend it as a useful addition to any physician's library.

**LIFE INSURANCE MEDICINE. A STUDY OF SOME OF ITS PROBLEMS AND THEIR RELATION TO CLINICAL MEDICINE.** By Members of the Medical Department of The New England Mutual Life Insurance Company. Volume 1. Cloth. Pp 219, with numerous tables and charts. Boston. New England Mutual Life Insurance Company, 1926.

To read this book is convincing proof that Life Insurance companies can and will write at least one chapter of "Medicine." The life insurance business has developed into one of the great commercial enterprises of our time, and naturally has accumulated a tremendous amount of certain types of invaluable information, specially applicable to many problems in preventive and clinical medicine. The value of statistics and data depends on their source, their accuracy and the honesty and intelligence of their interpretation, and there is no source from which the volume is so great, intelligent experience in their use so available or where there is less excuse for dishonesty of interpretation as the great mass of information accumulated by life insurance companies. It is true that they deal largely with selected groups, but comparisons are made with other groups, with census figures and other statistics. It is already clearly shown that gains in "expectation of life" have been largely limited to that group of diseases classed as infectious, while in those classed as circulatory, there has been a distinct loss. One interesting hypothesis is formulated in this connection, to wit: "The incidence of circulatory disease is in inverse relation to the amount of physical exercise which the group takes in the open air and, other things being equal, it is in direct relation to the amount of nervous and mental strain." Often the question of acceptability of a risk is decided on the result of a simple single test, and practical experience has justified this method of selection. Perhaps no better opportunity exists for the recognition and study of early signs and symptoms of disease than a careful examination of large numbers of applicants for insurance.

Eight extensive papers are presented on such varied subjects as preventive medicine, periodic health examinations, glycosuria, hypertension and longevity, the creatinine content of the urine and others. An extensive bibliography is appended to each chapter.

**PNEUMOCONIOSIS (SILICOSIS). A ROENTGENOLOGICAL STUDY WITH NOTES ON PATHOLOGY.** By HENRY K. PANCOAST, M.D., Professor of Roentgenology, University of Pennsylvania, and EUGENE P. PRENDERGRASS, M.D., Associate Professor of Roentgenology, University of Pennsylvania. Cloth. Price, \$4. Pp 186, with 23 illustrations. New York. Paul B. Hoeber, 1926.

This is an elaboration of an article dealing with the roentgenologic aspect of pneumoconiosis which was published by the authors in the *Journal of Roentgenology and Radium Therapy* in November, 1925. It is here presented in the form of a monograph and deals particularly with roentgen-ray studies of various types of the disease. There are chapters devoted to dusts, dusty occupations, disease and preventive measures. There are numerous reproductions of radiographs which are well chosen, are printed on good paper and have

excellent explanatory legends. The authors classify the disease roentgenologically into three stages, the first stage is characterized by a definite increase in the prominence and extent of the shadows of the hilum of the central zone, a thickening of the trunk shadows of the mid zone and an increased prominence of the linear markings of the peripheral zone, the second stage is characterized by a typical mottling throughout the lungs, caused by small fibrotic nodules varying greatly in size from that of a pinhead to that of a pea, more or less symmetrically arranged. There is often some interference with diaphragmatic excursions particularly the inner portions, the third stage is characterized by a diffuse fibrosis of varying type and degree, at times even "massive," with emphysema, pleural thickening, dense fibrous bands often wide and connected with marked deformities of the diaphragm and associated with restriction of diaphragmatic movements. The differential diagnosis from tuberculous conditions is discussed. A partial but well selected bibliography is appended.

MODERN MEDICINE, ITS THEORY AND PRACTICE, IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS. Edited by SIR WILLIAM OSLER, ed 3 revised. Re-edited by THOMAS McCRAE, assisted by ELMER H. FUNK. Volume 2. Pp 891 with illustrations. Price, \$9. Philadelphia: Lea & Febiger, 1925.

This volume includes the discussion of diseases of doubtful etiology, those caused by protozoa, spirochetes and animal parasites, diseases due to physical, chemical and organic agents, and deficiency diseases. Revision of all of the chapters has brought the subject matter up to date. This has been done for the most part by the original contributors. The former chapter on syphilis by Osler has been revised by Lewis A. Conner, and the one on yellow fever by Carroll has been rewritten by Thomas McCrae. The authoritative character of the original work is retained throughout. Of special interest are the chapters on smallpox by Beardsley, on vaccination by Dock, on measles by Ruhrah, on typhus fever by McCrae, on malaria by Craig, on syphilis by Osler, Churchman and Conner and on diseases caused by animal parasites by Stiles. The chapters devoted to deficiency diseases include the important discoveries of the past few years. Although definite progress has been made in this field, much remains obscure. The revised chapters naturally reflect the incompleteness of our knowledge of these subjects.

This volume, indeed the complete work, should find a place in every medical library.

IMMUNISATION LOCALE. By A. BESREDKA. Pp 252. Price, 20 francs. Paris: Masson and Cie, 1925.

In this monograph Besredka presents a fascinating survey of the work of his school in its relation to local immunization. Incidentally, he has developed at some length his views on many phases of natural and acquired immunity. Starting from the observation that in staphylococcus, streptococcus and anthrax infections physicians deal primarily with a skin infection, and that with cholera, dysentery and typhoid they deal with a gastro-intestinal infection irrespective of the avenue of infection (intravenous, intraperitoneal, subcutaneous or by mouth), he develops the thesis that the protective immunization against these infections should be developed chiefly in the respective tissues. For immunization by mouth he has insisted repeatedly on the use of bile in preparing the way so that proper contact may be made with the bacteria ingested and the mucous membrane which is to be immunized. Interesting is his conclusion that the humoral antibodies play a relatively minor role in protection against disease, an opinion that has won much ground among immunologists in general, but which still seems novel to many clinicians.

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## STUDIES IN ACROMEGALY

### VI THE DISTURBANCES OF CARBOHYDRATE METABOLISM <sup>†</sup>

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#### INTRODUCTION

In preceding papers in this series the subject which we here propose to discuss more in detail has already been touched on. It has been stated <sup>1</sup> that in our series of 100 personally observed cases of acromegaly one out of four has shown glycosuria, and approximately one out of eight proved to have clinically outspoken diabetes mellitus. It has also been stated, in a report dealing with the postmortem observations in four of these cases, <sup>2</sup> that one of the patients had apparently recovered from

<sup>†</sup> From the Surgical Clinic of the Peter Bent Brigham Hospital, Boston

1 Davidoff, L. M. Studies in Acromegaly. II Historical Note, Endocrinology **10** 453, 1926, III The Anamnesis and Symptomatology in 100 Cases, Endocrinology **10** 461, 1926

2 Cushing, H., and Davidoff, L. M. Studies in Acromegaly, V The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of their Significance, Monograph 22, Rockefeller Inst. M. Research, 1927

severe diabetes, whereas another had died in diabetic coma, the pancreatic islets in both of these cases having been regarded as histologically normal.

In another paper <sup>3</sup> we have ventured to discuss the question of the increased basal metabolic rate in acromegaly and have been inclined to interpret it as primarily of hypophysial origin, even though the thyroid may play a secondary rôle. The same or similar questions arise in regard to the diabetes of acromegaly. Is it primarily hypophysial and secondarily pancreatic, or are the two maladies—one hypophysial and the other pancreatic—merely coincidental? In either case, does the diabetes of acromegaly behave and run the same course as does the more common form of diabetes? An effort to answer these questions will be made in the present communication.

*Incidence*—The frequency of diabetes mellitus in acromegaly has been variously estimated. Arnold <sup>4</sup> found 9 per cent of diabetic cases in his review of fifty-six cases from the literature, Hansemann <sup>5</sup> found approximately 12 per cent among ninety-seven reported cases, and Hinsdale <sup>6</sup> found 11 per cent in 130 cases. Borchardt,<sup>7</sup> on the other hand, in a tabulation of 176 cases recorded up to 1908, found sixty-three (35.5 per cent) to have frank diabetes and eight more to have alimentary glycosuria showing a lack of carbohydrate metabolism in approximately 40 per cent of all cases.

The variability of these percentages doubtless depends a good deal on what the compiler of the statistics has been willing to accept as "diabetes mellitus." Borchardt was dealing, up to 1898, with practically the same reported cases of acromegaly that were studied by Hinsdale, and it is hardly likely that the incidence of diabetes in the disease had more than trebled between 1898 and 1908. For purposes of emphasis he may have been tempted to include as examples of diabetes some which others might question. In our series of personally observed cases the percentage that showed indubitable diabetes proves to be the same as that reported by Hansemann.

It, however, is undoubtedly true that if our 100 acromegalic patients had been under constant surveillance, melituria would have been observed in more than 25 per cent of them. Indeed, four of the twelve with frank diabetes showed no evidence of the disease during their first hospital sojourn, and only because they happened to be observed again at a later

3 Cushing, H., and Davidoff, L. M. Studies in Acromegaly. IV. The Basal Metabolism, *Arch. Int. Med.* **39** (May) 1927.

4 Arnold, J. Weitere Beiträge zur Akromegaliefrage, *Virchows Arch. f. path. Anat.* **135** 1, 1894.

5 Hansemann, D. Ueber Akromegalie, *Berl. klin. Wchnschr.* **34** 417, 1897.

6 Hinsdale, G. Acromegaly (Boylston Prize Essay), *Medicine* **4** 441, 1898.

7 Borchardt, L. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, *Ztschr. f. klin. Med.* **66** 332, 1908.

date was this complication disclosed. Furthermore, the fact, to be discussed later, that acromegalic patients, even in the absence of glycosuria, are apt to show a slight hyperglycemia, may indicate a predisposition on the part of most victims of the disease toward the development of diabetes.

Even should we accept the incidence of true diabetes in association with acromegaly as no higher than 12 per cent, the percentage is far greater than with any other known disorder. One naturally looks, therefore, for some single etiologic factor which might account for this peculiar association of two clinically distinctive maladies.

#### ETIOLOGY

Several hypotheses have been advanced for the glycosuria so often an accompaniment of acromegaly. They may be divided under two headings: (a) the neurogenic and (b) the endocrine.

*A The Neurogenic Explanations of the Glycosuria*—There are two of them. One ascribes the complication to pressure of the hypophysial tumor against a predicated sugar center in the hypothalamus, the other ascribes it to some autonomic nerve impulses possibly of emotional character. The first view, which was advanced nearly thirty years ago,<sup>8</sup> has gained such general credence in textbooks that Dock even makes the statement:<sup>9</sup> "Diabetes is most marked with the largest [pituitary] tumors." So far as we can see, there is nothing whatever to support this hypothesis.

That there are important centers in the hypothalamic region which have some bearing on the production of the other variety of diabetes, has been conclusively shown by Camus and Roussy,<sup>10</sup> and by Bailey and Bremer<sup>11</sup> from this clinic. But diabetes insipidus and diabetes mellitus are merely symptoms (one tasteless and one sweet, as pointed out by Thomas Willis) of two disorders which have no possible etiologic relationship, and it is unfortunate that they should continue to carry the same family name. It nevertheless is curious that they should come to be discussed together in connection with the disease acromegaly.

Of the two forms of diabetes, diabetes insipidus, though the rarer, is far more entitled to be considered as a hypophysial or parhypophysial symptom than is diabetes mellitus. But when one considers that diabetes insipidus is practically unknown as a complication of

8 Loeb, L. Beitrage zur Lehre von Diabetes Mellitus, *Centralbl f. innere Med.* **9** 893, 1898.

9 Dock, G. The Pituitary Body, in Osler, W., and McCrae, T. *Modern Medicine*, Philadelphia, Lea & Febiger, 1915, vol. 4, p. 812, Chapter XXI.

10 Camus, J. E., and Roussy, G. *Experimental Researches on the Pituitary Body*, *Endocrinology* **4** 507, 1920.

11 Bailey, P., and Bremer, F. *Experimental Diabetes Insipidus*, *Arch. Int. Med.* **28** 773 (Dec.) 1921.

pituitary adenomas, whether acromegalic or hypopituitary, no matter how large they grow to be or how much they may chance to deform the infundibulum and third ventricle, we may well pause before ascribing diabetes mellitus to the pressure of a pituitary adenoma against some still more hypothetical nerve center in the neighborhood. And of this we may speak the more emphatically since the far more numerous chromophobe adenomas of comparable size are rarely accompanied by glycosuria.<sup>12</sup>

In short, the size of tumor and the pressure against the brain as a cause of the diabetes can be entirely discounted. The essence of the matter lies in the fact that only one particular variety of adenoma, irrespective of its size, is prone to cause the disturbance of sugar metabolism which may go on to the production of diabetes mellitus. This particular kind of adenoma is that composed of chromophilic cells which accompanies acromegaly.<sup>13</sup>

One, however, cannot dismiss the hypophysial polyurias and, more particularly, the encephalic glycosuria in quite so summary a fashion. It has long been known that a transient glycosuria is a frequent accompaniment of basal fractures of the skull which may possibly be due, as one of us pointed out,<sup>14</sup> to a coincidental contusion of the pituitary body. Some recent studies by Davidson and Allen<sup>15</sup> have shown that even in the absence of glycosuria, determinations of blood sugar on patients after injuries of the head show a temporary relative intolerance for glucose. All those, moreover, who have undertaken to perform experimental hypophysectomies will have observed that certain of the animals show a transient postoperative glycosuria whether or not they subsequently develop the prolonged and excessive polyuria resembling clinical diabetes insipidus. We have learned from the time of Bernard that various piqûres evoke glycosuria, and we also know that emotional

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12 Anders and Jameson (*Am J M Sc* **148** 323, 1914) report several such cases, but most of them showed only a slight transient glycosuria or a terminal one associated with increased intracranial pressure. One case of hypopituitarism with true diabetes was reported by Sainton and Rol (*Rev neurol* **25** 785, 1913), and they quote a similar observation by Debove. Rare case reports of diabetes coincidental with unusual lesions of the hypophysis such as gumma (Cushing, 1912) or tuberculoma (Lucien et Parisot, 1909) are too infrequent and bizarre to be of significance in this discussion. Whereas 25 per cent of the 100 acromegalic patients in the Brigham Hospital series showed or had a history of melituria, only four of 168 patients with hypopituitary symptoms and a surgically verified chromophobe adenoma either showed or gave a history of melituria.

13 Bailey, P., and Davidoff, L. M. Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly, *Am J Path* **1** 185, 1925.

14 Cushing, H. The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, p. 265.

15 Davidson, E. C., and Allen, C. I. The Blood Glucose Curve in Head Injuries, *Bull Johns Hopkins Hosp* **37** 217, 1925.

impulses may serve to produce a hyperglycemia with the discharge of sugar, but it is hardly to be believed that the diabetes of acromegaly is due to any such cause or causes

*B The Endocrine Explanation of the Glycosuria*—Under this heading we must consider the thyroid, suprarenals, islets of Langerhans and hypophysis as possible agents which independently of one another, or together, may disturb the carbohydrate metabolism of the body

The notion that an increased activity of the thyroid is responsible for acromegalic diabetes mellitus was first expressed by Lorand<sup>16</sup>, and, to be sure, not only is an enlarged thyroid common in acromegaly, but the increased metabolism so often seen might be regarded as an additional evidence of hyperthyroidism. But diabetes mellitus is not a common complication of hyperthyroidism even though transient glycosurias and a tendency toward hyperglycemia are frequently observed, nor does the reverse condition, myxedema, experimental or clinical, show an increase of carbohydrate tolerance in any way comparable to the marked increase seen in experimental or clinical hypopituitarism. What is more, the enlarged thyroid in acromegaly is usually of the inactive or colloidal type.

We consequently may disregard the thyroid as a possible primary agency, and no more does the suprarenal deserve serious consideration, for though the suprarenal cortex hypertrophies in acromegaly, it is the product of the medullary substance, epinephrine, which, under the influence of the autonomic nervous system, is capable of mobilizing sugar with the production of a transient glycosuria.

We may therefore confine ourselves to the hypophysial and pancreatic aspects of the subject in an attempt to answer the question propounded in the introductory paragraphs as to whether acromegalic diabetes differs appreciably from the primarily pancreatic form of the malady.

The senior author in collaboration particularly with Goetsch and Jacobson,<sup>17</sup> and Jacobson and Weed,<sup>18</sup> was engaged for several years in the elusive pursuit of the hypophysial glycosuric and nonglycosuric polyurias. These studies were undertaken after it had been observed that a temporary glycosuria was apt to follow a hypophysectomy, and it was at the time<sup>19</sup> anticipated that the animals would continue to show

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16 Lorand, A. Pathogenie du diabète dans l'acromégalie, *Compt rend Soc. de biol.* **56** 554, 1904

17 Goetsch, E., Cushing, H., and Jacobson, C. Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, *Bull Johns Hopkins Hosp* **22**·165, 1911

18 Weed, L. H., Cushing, H., and Jacobson, C. Further Studies on the Rôle of the Hypophysis in the Metabolism of the Carbohydrates, *Bull Johns Hopkins Hosp* **24** 40, 1913

19 Cushing, H. The Hypophysis Cerebri. Clinical Aspects of Hyperpituitarism and of Hypopituitarism, *J A M A* **53**·249 (July 24) 1909

a lowered assimilation limit for sugars as a consequence of the operation. Much to our surprise, quite the reverse effect was observed, for the hypophysectomized animals gradually acquired a high sugar tolerance and often showed slight hypoglycemia<sup>20</sup>. This, to be sure, is what might have been expected if the experimental states of hypopituitarism are the reverse of acromegaly, in which, as we now know, glycosuria and hyperglycemia are common. But at the time these studies were under way this was not very clear, and the possible mistake was made of ascribing the disturbance of sugar metabolism to a posterior rather than to an anterior lobe effect.

Certain other experiments were undertaken which showed that an experimentally induced hyperglycemia, brought on by removal of a large portion of the pancreas, tended to subside when a partial hypophysectomy was subsequently performed, and, conversely, that when animals had acquired a high sugar tolerance with hypoglycemia after hypophysectomy, they bore the removal of a large portion of the pancreas with less disturbance to their carbohydrate balance than would the normal animals. Since these observations suggested a close interrelation of an opposing sort between the hypophysis and the pancreatic islets, it was stated<sup>17</sup>: "If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the secretion of the hypophysial posterior lobe [sic] greatly enhances their power in this respect." In other words, it was appreciated that extracts of the pancreatic islets and of the hypophysis should theoretically at least counteract each other in their metabolizing effect on the carbohydrates. Let us consider this matter first from the standpoint of the pancreas.

#### RELATION OF THE PANCREAS TO THE ACROMEGALIC GLYCOSURIAS

Unfortunately, the universally accepted view that the islets of Langerhans are functionally deranged in pancreatic diabetes has not as yet found its anatomic counterpart, or at least one which is wholly satisfactory. Cecil<sup>21</sup> in a study of the pancreas in ninety cases describes the finding of lesions of one sort or another in 88 per cent of them. Fibrosis of varying degrees was present in seventy-six cases, hyaline degeneration in twenty-seven, lymphocytic infiltration in nine, and hypertrophy in thirty-four cases. A recent report of twenty-six personally studied autopsies leads Root and Warren<sup>22</sup> to admit that, "No one distinctive

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20 Crowe, S. J., Cushing, H., and Homans, J. Experimental Hypophysectomy, *Bull. Johns Hopkins Hosp.* **21** 127, 1910.

21 Cecil, R. L. A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, *J. Exper. Med.* **11** 266, 1909.

22 Root, H. F., and Warren, S. A Clinical and Pathologic Study of Twenty-Six Cases of Diabetes, *Boston M. & S. J.* **194** 45, 1926.

lesion of the islands was found" They, however, describe varying degrees of hyalinization in half of the cases, some sclerosis and lymphocytic infiltration in five others, and in three an adenomatous enlargement Nevertheless, there is no gainsaying that the pancreas must often be thoroughly searched to find these lesions and, even when found, apparently normal islets may exist alongside of those affected

Even less definite if anything have been the descriptions of the histopathologic lesions of the pancreas in acromegalic diabetes as reported in the literature Some of the early and much quoted autopsy reports, to be sure, such as those by Hansemann,<sup>23</sup> Dallemagne<sup>24</sup> and Pineles,<sup>25</sup> record pancreatic lesions, but these lesions consisted merely of an increase in the interlobular connective tissue which is not at all incompatible with normally functioning islets How little bearing these sclerotic changes have on the subject is well illustrated by two of the carefully studied cases reported by Fraenkel, Stadelmann and Benda,<sup>26</sup> one of them showed no clinical diabetes, but at autopsy had a marked interlobular sclerosis of the pancreas, whereas the other had marked clinical diabetes, died in diabetic coma, and a perfectly normal pancreas was found post mortem Pathologic evidence prior to Opie's discovery in 1901 is, however, at the best of little value

Specific reference to the condition of the pancreatic islets in the report of cases of acromegaly with diabetes which have come to autopsy has been rare One of the earliest references to the subject appears to have been made by Norris<sup>27</sup> who described an adenoma-like hypertrophy, and Kraus<sup>28</sup> reported a case of long standing, in which definite sclerosis of the islets was disclosed In a previous paper in this series,<sup>2</sup> we have described the findings in two of our own cases One of the patients had apparently recovered from severe diabetes, the other had died in diabetic coma In both, the islets had been pronounced normal by competent pathologists A reexamination of the sections at the present time shows that the islets in the recovered cases are perhaps hypertrophic, and in the case of the patient who died in coma one single islet shows

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23 Hansemann, D Die Beziehungen des Pankreas zum Diabetes, *Ztschr f klin Med* **26** 191, 1894

24 Dallemagne, M Trois cas d'acromegalie avec autopsie, *Arch de med exper et d'anat path* **7** 589, 1895

25 Pineles, F Die Beziehungen der Akromegalie zum Myxodem und so anderen blutdrusener Krankheiten, *Volkman's Samml, N F*, 1899, no 242, p 1421

26 Fraenkel, A, Stadelmann, E, and Benda, C Klinische und anatomische Beitrage zur Lehre von der Akromegalie, *Deutsche med Wchnschr* **27** 513, 536, 564, 1901

27 Norris, C A Case of Acromegalia, *Proc New York Path Soc* **7** 19, 1907-1908

28 Kraus, E J Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zueinander unter normalen Verhaltnissen und in Tumoren, *Beitr z Path Anat u z allg Pathol* **58** 159-210, 1914

what may possibly be a strand of sclerosis—certainly nothing in either case on which a diagnosis of existent or preexistent diabetes could definitely be based. Of course death in diabetic coma by no means signifies that the patient had, at the time, advanced diabetes, and the absence of pathologic changes therefore does not mean much in a single case.

It is conceivable that the oversecretion of the hypophysial substance may indirectly produce glycosuria in one of two ways (1) by neutralizing the secretion of the islet tissue in circulation, thereby causing compensatory hypertrophy with ultimate exhaustion of the cells of Langerhans leading to the degenerative changes with which we are familiar, or (2) by actually checking the secretory function of the islets which might possibly lead to no histopathologic changes. However this may be, it seems wholly improbable that the diabetes in acromegaly is due to an independent and coincidental lesion, functional or otherwise, of the pancreatic islets.

TABLE 1—*Blood Sugar*

	Case 1	Case 2	Case 3	Case 4
Fasting	0.38%	0.286%	0.13%	0.15%
	20 units insulin subcutaneously	10 units insulin intravenously*	20 units insulin subcutaneously	20 units insulin subcutaneously
After 2 hours	0.27	0.227	0.10	0.109
After 4 hours	0.25	0.189	0.10	0.093

\* This patient had breakfasted after the fasting blood test.

If it is to be assumed, then, that in the state of hyperpituitarism a substance antagonistic to insulin is thrown into the circulation, it must also be assumed that any additional insulin supplied to a patient with acromegalic diabetes will serve to lower the blood sugar just as it would in ordinary diabetes, in other words, it would overcome the action of the excessive pituitary secretion. To test this, observations in four acromegalic patients with diabetes were carried out in the following manner. Fasting blood sugar determinations were made, insulin was injected and the blood sugar quantitated at varying intervals afterward.<sup>29</sup> The results are shown in table 1.

Dr. Fitz has expressed doubt as to whether the fall in the sugar percentage in one or two of these cases has been as significant as he would have expected in ordinary diabetes. Blum and Schwab,<sup>30</sup> on the other hand, made a similar test on two diabetic patients, one with

<sup>29</sup> The sugar determinations according to the method of Folin and Wu have been made for us in the laboratory of our colleague, Dr. Reginald Fitz, to whom we wish here to express our great indebtedness not only for this service but also for his continued interest and helpfulness in other matters relating to the problem of these glycosurias.

<sup>30</sup> Blum, L., and Schwab, H. *Diabete acromegalique et insuline*, Compt rend Soc de biol 89 195, 1923.

acromegaly and one without, and found that the sugar content of the blood became reduced just as promptly and effectively in the acromegalic as in the other patient. We may therefore conclude that insulin acts favorably on the hypophysial as well as on the pancreatic form of the disease, but whether the diabetes of acromegaly is as definitely controlled by insulin is questionable. To this we shall return.

Observations on the possible reciprocal action of pancreatic lesions on the hypophysis have been reported by several writers, but the results have been conflicting. Mention has been made of the experiments by Goetsch, Cushing and Jacobson<sup>17</sup> in which histologic changes, particularly shown by an increased cellularity of the posterior lobe, were described as a consequence of subtotal pancreatectomies. The observations were thought to indicate a hypertrophic reaction.

The same authors, as previously stated, showed that an animal primarily subjected to a subtotal pancreatectomy, and subsequently to a subtotal hypophysectomy, ultimately acquired an increase of tolerance for glucose over that which existed before either operation was done. This would seem to indicate that an insulin deficiency with hyperglycemia may be more than compensated for by the production of a secondary hypophysial deficiency. In support of these experimental results are the observations of Fry<sup>31</sup> who examined the pituitary glands of eight diabetic patients and described certain changes in the hypophysis, such as an increase in eosinophilic cells and excess of colloid, which were interpreted as evidencing hyperactivity.

The experiences of others to the contrary are more in accord with what our present knowledge of the subject would lead us to expect—namely, retrogressive rather than hypertrophic changes in the hypophysial anterior lobe. Thus Kraus<sup>32</sup> examined the hypophysis in twenty-three cases of diabetes, such changes as were found to exist were limited to the eosinophilic elements of the anterior lobe and were thought to be degenerative. Believing that underactivity of the anterior lobe produces an increase in carbohydrate tolerance, he explained the changes on the basis of a self-regulatory and interglandular carbohydrate mechanism. Vernon<sup>33</sup> also found degenerative changes in the hypophysis in three out of six diabetic patients.

We may therefore conclude from the several, though in part contradictory observations mentioned in this section, that the pancreas and probably its islet tissue exerts a reciprocal effect on the hypophysis, that both pancreatic islets and hypophysis have some influence on sugar

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31 Fry, H. J. B. The Pituitary Gland in Diabetes Mellitus and Disorders of Glands of Internal Secretion, *Quart. J. Med.* **8** 278, 1915.

32 Kraus, E. J. Hypophyse und Diabetes Mellitus, *Virchows Arch. f. path. Anat.* **228** 68, 1920.

33 Vernon, O. Ueber die Bedeutung der Hypophyse in der Pathogenese des Diabetes Mellitus, *Centralbl. f. allg. Pathol. u. path. Anat.* **31** 521, 1921.

metabolism, that insulin serves to affect favorably both acromegalic and pancreatic forms of the disease, and that a hypophysectomy may offset experimentally produced pancreatic diabetes. We may now turn to a consideration of the subject of the glycosurias from the primary standpoint of the hypophysis.

#### RELATION OF THE HYPOPHYSIS TO THE GLYCOSURIAS

The first evidence that prompts us to expect such a relationship is, as noted at the outset, the frequency of glycosuria, variously estimated from 25 per cent to 40 per cent in acromegalic patients. Since the conclusions, based largely on clinical and circumstantial evidence, that acromegaly is an expression of hyperfunction of the pituitary have been conclusively supported by the experiments of H. M. Evans and his co-workers,<sup>34</sup> the hyperglycemia and glycosuria found in association with acromegaly, if at all related to the hypophysis, must be a result of its overactivity, and what is more, they must be associated with oversecretion of the acidophilic cells of the pars anterior.

On an experimental basis little has as yet been done to substantiate this statement, which rests largely on clinicopathologic deductions. Borchardt<sup>7</sup> made parenteral injections of saline extracts of fresh equine pituitary glands into thirty rabbits with a resulting glycosuria in twenty-three and a hyperglycemia in two of the animals. The effect of similar injections in dogs was less striking. In his experiments, unfortunately, the posterior lobe was included in the extract.

Miller and Lewis<sup>35</sup> injected pituitary extracts into thirty small dogs, half of them given anterior lobe and half posterior lobe extracts. Glycosuria occurred in three animals, and two of these had received anterior lobe injections.

Goetsch, Cushing and Jacobson<sup>17</sup> in their studies on the sugar tolerance of hypophysectomized animals observed that the high tolerance for glucose shown by some of their animals, and found to be accompanied by hypoglycemia, could be overcome and glycosuria produced by the hypodermic injection of anterior as well as of posterior lobe extracts. Since the discovery of insulin, Houssay and Magenta<sup>36</sup> have reported that hypophysectomized dogs which recover with symptoms of glandular insufficiency are much more sensitive to the effects of the injection of insulin than normal animals, and are easily rendered hypoglycemic.

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34 Evans, H. M. *The Function of the Anterior Hypophysis*, Harvey Lecture Series, Philadelphia, 1923-1924, p. 212.

35 Miller, J. L., and Lewis, D. *The Frequency of Experimental Glycosuria Following Injections of Extracts of the Hypophysis*, Arch. Int. Med. **9**: 601 (May) 1912.

36 Houssay, B. A., and Magenta, M. A. *Sensibilidad en los perros hipofisoprivos a la insulina*, Rev. Asoc. med. argent. (Soc. de Biol.) **37**: 389, 1924, Compt. rend. Soc. de Biol. **92**: 822, 1925.

These corroboratory observations would lead one to suppose that in the opposed condition of experimental hyperpituitarism the animals would be much less sensitive. So far as we are aware, however, no studies have as yet been made on the blood or urine of Evans' rats or of other animals given injections over long periods with active anterior lobe extract. We may assume that they will show hyperglycemia.

On clinical grounds attention may be called to the frequent occurrence of glycosuria in pregnancy (11.8 per cent according to Reichenstein), during which, as first demonstrated by Erdheim and Stumme<sup>37</sup> the hypophysial pars anterior enlarges and takes on additional activity, indeed repeated pregnancies may be the forerunner of acromegaly, as is well known. Attention may be called also to the not infrequent appearance of glycosuria in the period of rapid growth associated with adolescence, which in all likelihood is an expression of the same pituitary activity responsible for the rapid increment of growth in acromegaly. That the combination may at times be puzzling to clinicians is exemplified by a case recently referred to the senior author by Dr. E. P. Joslin. The story follows:

Richard M. is a boy 8 years of age who looks easily 14. He is 53 inches tall (5 inches over the average for his age) and weighs 79 pounds (average for his age, 54 pounds). He has been in perfect health, is an exceptional student and the leader in his school. He was accidentally found to have 5 per cent sugar in his urine. This disappeared under treatment with insulin. The question arises whether this is primarily pancreatic or primarily hypophysial diabetes. The roentgen ray shows a normal sella.

Another question which might be raised by such a case is whether the recognized peak of diabetes in childhood at about 14 years is in any way related to a period of unusual activity of the anterior hypophysis. On the contrary, it is not inconceivable that the pancreatic diabetes of childhood may secondarily stimulate the anterior hypophysis, which would be in accordance with Fry's observations<sup>38</sup>.

The injection of such a case into this discussion may appear to be remote from the subject of acromegaly but, after all, the hormone is probably the same whether gigantism or acromegaly or mere overgrowth is produced. Experience has taught us that pituitary insufficiency whether clinical or experimental is accompanied by a high sugar tolerance, or expressed in the terms of Houssay's experiments, just mentioned, in leaving the patient more sensitive to insulin. We are inclined to believe too, on theoretical grounds as well as on the grounds of experience, that patients with hyperpituitarism (acromegaly) are on the other hand less sensitive to insulin than normal persons.

37 Erdheim, J., and Stumme, E. Ueber die Schwangerschaftsveränderung der Hypophyse, *Beitr. z. Path. Anat. u. z. allg. Pathol.* **46** 1, 1909.

38 Dr. Joslin informs us that a study of 100 diabetic children shows them to average 2.7 inches above the standard height at the onset of their disease.

*The Counteraction of Pituitary Extracts and Insulin*—The antagonism of these two substances was first pointed out in an important article by J H Burn<sup>39</sup> The observation has been supported by the experience of the clinic In three of our patients with acromegalic diabetes who had been shown to respond normally to insulin, 20 units of insulin combined with 1 cc of solution of pituitary, U S P (the brand used was pituitrin, P D & Co ) were injected The results are given in table 2 and show that the expected fall in blood sugar at the end of a two hour period had not occurred

These figures confirm Burn's interesting disclosure that the two substances are mutually antagonistic It was also shown by Burn that pituitary extract would counteract the hypoglycemic reaction in animals of over dosage with insulin, and this has proved of benefit in clinical cases One would expect, therefore that the injection of pituitary extract alone would greatly increase the blood sugar The test was made on case 2 cited in table 2, and though a definite increase in blood

TABLE 2—*Blood Sugar*

	Case 1	Case 2	Case 3
Fasting	0 33%	0 13%	0 15%
	20 units insulin + 1 cc solution of pituitary subcutaneously	20 units insulin + 1 cc solution of pituitary subcutaneously	20 units insulin + 1 cc solution of pituitary subcutaneously
After 2 hours	0 32	0 14	0 142
After 4 hours	0 30	0 12	0 112

sugar was observed four hours after the injection, it was less than we had expected This is a matter which deserves further study, but the single clinical observation recalls the experiences of Burn, who states that posterior lobe extract when given by itself to his experimental animals failed to produce a rise in blood sugar sufficient to explain the inhibition of the action of insulin when the two substances were injected together

Ellis,<sup>40</sup> in an interesting report of a case in which the diabetes of acromegaly had disappeared after a successful hypophysectomy, theorizes on the cause of the glycosuria and suggests that it is due to an increased activity probably of the pars intermedia, whose extract, like that of the pars nervosa, inhibits the normal action of insulin on carbohydrate metabolism He based this hypothesis on the statement of H M Turnbull that acromegalic adenomas arise from this intermediate portion of the gland, whereas the view generally accepted is that they arise

39 Burn, J H The Modification of the Action of Insulin by Pituitary Extract and Other Substances, *J Physiol* **57** 318, 1923

40 Ellis, A W M Hyperglycaemia and Glycosuria in Acromegaly with Pathological Report by Prof H M Turnbull, *Lancet* **1** 1200, 1924

from the acidophilic cells of the anterior lobe. Other than for this apparent point of discord we find ourselves in agreement with the author's interpretation of his case.

This mention of the seat of origin of the chromophile adenomas brings up another question for which as yet there is no reasonable answer. Why should posterior lobe extracts be those to counteract insulin when, so far as is known, hyperpituitarism, which alone of hypophysial diseases provokes glycosuria, is an anterior lobe disorder? This is but one of the many apparent contradictions met with in the study of pituitary function, the key to which is not as yet in our hands.

As a matter of fact, we know little about the source or nature of the actual substance found in the posterior lobe, familiar as we may be with its many functions. Whether the cells of the pars anterior or pars intermedia play any part in the formation of the active principle of the posterior lobe is unknown, though histologic preparations of the hypophysis in certain conditions of disease suggest that they may, and though we are loath to lay any particular stress on the finding, it may be stated that in two of the acromegalic hypophyses in our collection the posterior lobe had become abundantly invaded by epithelial cells. It possibly may come to be shown that the posterior and anterior lobes have interdependent rather than the quite separate functions generally ascribed to them.

One thing obviously remains to be done, namely, to test the counter-effects on insulin of an active anterior lobe extract simultaneously injected. This has been tried by Buin with negative results in animals, and unfortunately no substance of this sort sufficiently free from protein and infectious material is yet available which can be used with safety on the human subject. We would be inclined to assume that an active anterior lobe substance might be even more directly antagonistic to insulin than the extract of the posterior lobe, but it may not prove to be so.

#### SUGAR TOLERANCE TESTS ON ACROMEGALIC PATIENTS WITHOUT GLYCOSURIA

In addition to the surprisingly high percentage of acromegalic patients that show either glycosuria or frank diabetes, we have observed that acromegalic patients who show no sugar in the urine may have a subnormal capacity to dispose of carbohydrates when given intravenously. In order to eliminate the variability in the degree of absorption of sugars given by the oral method, the glucose tolerance test that was finally adopted by us for the purpose of this study was as follows:

Early in the morning while fasting, the patient was weighed and a specimen of urine voided. Blood was taken for a fasting blood sugar determination and

immediately thereafter a purified 20-25 per cent glucose solution in normal saline was injected intravenously, the period of injection lasting from fifteen to twenty minutes, depending on the quantity used. The amount was determined by the patient's body weight, 0.5 Gm of glucose per kilogram being used. Blood was then removed for sugar tests at one-half, one and two hour intervals following the injection. The urine sugar was quantitated at the end of the two hours.

The blood sugar curves obtained in ten tests of this sort performed on nine patients with acromegaly, two of whom had a mild degree of diabetes mellitus are shown in chart 2. It will be seen from this graph that all the curves rise above the normal one, and, with a single exception, remain higher than the normal throughout the period of examination. Eliminating from consideration the two patients with clinical diabetes, in whom a decreased tolerance for glucose would naturally be expected, it would appear that a tendency exists among all the other seven toward a similar intolerance.

The literature contains few examples of tests of this sort made on patients under similar circumstances, namely, intravenous injection of glucose into acromegalic patients without diabetes. Perhaps the first sugar tolerance test to be carried out on such a patient, the oral method having been used, was by Strumpell<sup>41</sup> who found glycosuria in his patient after the ingestion of only 100 Gm of glucose.

Wilder and Sansum<sup>42</sup> report on five pituitary cases—two acromegalic cases, one case of "suspected gigantism" and two with "dyspituitarism showing Frohlich's syndrome." Their tests were carried out by the use of apparatus which permitted the continuous injection of a given percentage of glucose at a uniform rate, and they took the tolerance level to be that just above which sugar appears in the urine. In a series of normal persons they established the fact that "glucose injected at the rate of 0.8 Gm per kilogram of body weight per hour caused no glycosuria, but in each case sugar appeared in the urine when the injection rate was 0.9 Gm per kilogram per hour." In their pituitary cases, on the other hand, they found that, "three showed a bare trace of sugar in the urine after the injection of 0.8 Gm per kilogram per hour, and all gave a definite glycosuria after receiving 0.9 Gm per kilogram per hour." Unfortunately, they fail to state, what is of greatest interest from our point of view, namely, which three of their five cases showed a lowered tolerance, but in the light of our observations the three concerned must have been the two cases of acromegaly and the case of "suspected gigantism."

41 Strumpell, A. Ein Beitrag zur Pathologie und pathologische Anatomie der Akromegalie, *Ztschr f Nervenheilk* **11** 51, 1897.

42 Wilder, R. M., and Sansum, W. D. d-Glucose Tolerance in Health and Disease, *Arch Int Med* **19** 311 (Feb) 1917.

Major<sup>43</sup> included one nondiabetic acromegalic patient in his studies on sugar tolerance, but his tests also were by means of oral administration of glucose, although followed by blood sugar determinations. He believed that his patient showed an increased sugar tolerance. His test, however, not only is open to the objection applicable to all tests carried out by the oral method of administration, but he also delayed one hour after the ingestion of the glucose before taking the first blood sugar reading, thus, as pointed out by Sachs and MacDonald,<sup>44</sup> missing the initial rise determinable at the end of half an hour. His patient, moreover, may have chanced to be in the stage of inactive acromegaly.

Two papers pertaining to the subject at hand have recently been written by H. J. John.<sup>45</sup> The earlier paper, which is concerned with the spontaneous disappearance of diabetes, contains two case reports, one of a typical acromegalic patient with diabetes who had failed previously to be benefited by insulin. After a renewed and more vigorous insulin regimen, the patient became sugar-free, and three months later a sugar tolerance test gave, to the author's "astonishment," a normal curve. The case was regarded as one of diabetes in which the acromegaly was merely coincidental. It, however, is included in John's second paper which deals more specifically with acromegalic diabetes, of which he reports two further examples. In one of them, briefly recorded as a case of acromegaly without glycosuria, it is nevertheless stated that "there was slight leaning toward impairment of carbohydrate function," as shown by a sugar tolerance test.

All this is quite in accord with our own views, but we find ourselves at variance with this author in his statement that 12 per cent of the patients in the Cleveland Clinic with *hypopituitarism* had more or less marked diabetes—in other words, as large a percentage of diabetic patients as is usually seen in *hyperpituitarism*. This is so contrary to the observations of others that one is led to query what conditions may have been classified as *hypopituitarism*. In the entire series of 168 patients from the Peter Bent Brigham Hospital with histologically verified pituitary adenomas recorded as "chromophobe," only four prove to have shown even a transient glycosuria. The tissues of these four cases have since been reinvestigated with special stains, and two of them at least are distinctly acidophilic in type. We are inclined to feel therefore that the presence of glycosuria or hyperglycemia with

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43 Major, R. H. Studies on Sugar Tolerance, *Bull. Johns Hopkins Hosp.* **34**: 21, 1923.

44 Sachs, E., and MacDonald, M. E. Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions, with a Review of Literature, *Tr. Am. Neurol. A.*, 1924, pp. 129-162.

45 John, H. J. Spontaneous Disappearance of Diabetes, *J. A. M. A.* **85**: 1629-1631 (Nov. 21) 1925, The Possible Relationship Between Acromegaly and Diabetes, *Arch. Int. Med.* **37**: 489 (April) 1926.

pituitary disease in the vast majority of cases implies hyperpituitarism, even though the clinical evidence of overgrowth may scarcely suffice to justify the term acromegaly as Pierie Marie employed it

This is a matter which we hope to consider at another time and place. It is safe to say, with the data at hand, that the majority of patients with acromegaly have difficulty in metabolizing carbohydrates, and that even in the absence of melituria, they tend to show a relative hyperglycemia in the active stages of the disease

#### THE COURSE AND PROGNOSIS OF ACROMEGALIC DIABETES

The belief seems to be widespread among those who have written about diabetes that the usual form of the disease differs in no respect from that which happens to be associated with acromegaly. This statement is explicitly made by John,<sup>46</sup> for example, who adds that a hypophysectomy has never been known to cure a patient of pituitary diabetes

To these two questions we may now pass. Does the diabetes of acromegaly differ from ordinary diabetes? Do hypophysectomies for the acidophilic adenomas of the disease serve to influence favorably the disturbed carbohydrate metabolism whether or not they may be regarded as effecting a cure?

The convictions of those best informed regarding the course and prognosis of ordinary diabetes may be fairly assumed to be contained in the statement of Fitcher in the last edition (vol 2, 1926, p 53) of Osler's "Modern Medicine," when he says

Generally speaking, the later in life the symptoms first manifest themselves, the better is the prognosis. The majority of cases after middle life run a chronic course, and it is not very uncommon to see stout, elderly individuals in whom the disease has lasted ten to fifteen years. Cases with hereditary influences are the most favorable. Once the disease is well established, it is seldom, if ever, that a permanent cure is effected

The introduction and perfection in the therapeutic use of insulin had raised the hope that means not only of alleviating but possibly of curing the diabetes had been found. We may still cling to the hope, for we do not yet know all that insulin may accomplish, but Harrison<sup>47</sup> concludes his careful investigation of the subject with the statement that "no case of diabetes mellitus has yet been published in which it was possible eventually to stop the insulin entirely and to allow an absolutely unrestricted diet without the return of hyperglycemia."

The contrast between these well established opinions and the course observed not only occasionally but frequently in the diabetes associated

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<sup>46</sup> John, H. J. The Possible Relationship between Acromegaly and Diabetes, *Arch Int Med* **37** 489 (April) 1926

<sup>47</sup> Harrison, G. A. Can Insulin Produce Even a Partial Cure in Human Diabetes Mellitus? *Quart J Med* **19** 223, 1926

with acromegaly is most striking. Long before Opie's discovery<sup>48</sup> of the relation between diabetes and the islands of Langerhans, observers were impressed by the bizarre fashion in which the glycosuria in cases of acromegaly would appear and disappear without relation to dietary restrictions. The point which was particularly emphasized by von Noorden<sup>49</sup> has been recognized by other writers on the subject, and is in full agreement with our many personal observations.

There is no difficulty in accounting for this fluctuating character of the acromegalic glycosurias. Hyperpituitarism as expressed by acromegaly is not a steadily progressive disorder and behaves in this respect much as does hyperthyroidism. There are distinct waves of what the patient recognizes as more or less intense periods of "acromegalism". Some patients with pronounced acromegaly go through a long life little troubled by these symptoms, others are continually more or less miserable from the toxic effects of the disease which may at times so closely resemble those of thyreotoxicosis that they may be subjected to thyroid extirpations on the mistaken idea that the goiter, which may be present, is the primary cause of the malady rather than a secondary effect. Still other patients may never have more than a single primary wave of transient hyperpituitarism, and such evidences of overgrowth as may have been occasioned remain barely discernible. Indeed the acidophilic adenoma which is unquestionably the underlying lesion may become completely degenerated and cystic, just as may a thyro-adenoma, and signs of actual pituitary insufficiency come to be superimposed on the relics of a once active acromegaly.

These clinicopathologic aspects of the disease appear to be scarcely appreciated or borne in mind by those who have, from a biochemic or physiologic standpoint, made reports on an isolated case or two. But with these peculiarities of the malady clearly before us, we may more easily appreciate how it happens that acromegalic patients may show waves of melituria, even periods which justify the designation of actual diabetes and yet spontaneously recover from them, irrespective of any dietary restrictions or treatment by insulin. One of our patients, an intelligent and observant woman, who had a transphenoidal operation twelve years ago with marked relief from her pressure symptoms, continues nevertheless to have recurrent periods of "acromegalism", and with each wave of the process, which is signalized by a sense of exhaustion, she becomes temporarily highly glycosuric.

Without a long series of cases studied with these characteristic periodicities of the malady in mind, it is obvious that the effects of an

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48 Opie, E. *Disease of the Pancreas, Its Cause and Nature*, Philadelphia, J. B. Lippincott Company, 1903.

49 Von Noorden, C. *Die Zuckerkrankheit und ihre Behandlung*, ed. 6, Berlin, 1912.

operation in itself may be most difficult to determine. For a crucial test not only must the operation have been a radical one and performed on a patient with pronounced melituria, but the patient must also be kept under observation for a long time and have repeated determinations of urine and blood sugar under varying conditions of activity and diet. These opportunities are rare.

In an earlier paper in the series<sup>2</sup> we have given in some detail the history of an acromegalic patient whose long-standing diabetes had disappeared, subsequent to, though not convincingly because of, a hypophysectomy. He at least had become sugar-free, with no dietary restrictions, a year later, when he died from cardiac failure with generalized anasarca. To illustrate further the difficulties of determining what credit if any may be ascribed to an operation rather than to other causes, when a patient who has once had melituria subsequently remains sugar-free on an unrestricted diet, the following case may be cited.

*Advanced acromegaly of about seven years' duration. Symptoms of diabetes of about twelve months. Control of diabetes by insulin. Transsphenoidal operation. No return of glycosuria for six months on an unrestricted diet.*

C S., an unmarried Greek man, aged 31, was referred to us by the Veterans' Bureau on Jan. 29, 1929. His illness began about 1919, with severe headaches, weakness, accession of weight, profuse sweats, increase in size of hands and feet, and diminution of sexual power.

He was a typical acromegalic with large extremities and features, mandibular prognathism, spaced teeth, hypertrichosis, hyperhidrosis, a ballooned sella, primary atrophy and beginning bitemporal hemianopia.

According to the clinical notes accompanying the case, the urine on one occasion in September, 1914, had shown a trace of sugar. The patient, however, gave a history of increased thirst and polyuria for a period of only about a year previous to admission.

On the day following his entry to the hospital his urine showed 5.5 per cent sugar, and his blood sugar was 0.25 per cent. While on an unrestricted diet, and in spite of his large appetite, his blood sugar in the course of three days dropped to 0.15 per cent and his urine sugar to 1.8 per cent. These levels were maintained for the succeeding two weeks. From February 14 to February 25 he was given insulin in increasing doses. Not until he had received twenty units twice a day did he become practically sugar-free. Insulin was then discontinued, and although he subsequently showed little more than a trace of sugar in the urine, he nevertheless continued to have a slight hyperglycemia.

Between the dates of February 28 and March 3 he had a severe tonsillitis with a temperature of 102 F. without affecting his condition, his blood sugar taken on one of these days was nearly 0.2 per cent although with only a trace of sugar in the urine.

He was followed through the month of March without any further change. On March 12, when his blood sugar showed 0.13 per cent and he had a trace of glycosuria, he was given 20 units of insulin coincidentally with 1 cc of surgical pituitrin. This caused a slight rise in his blood sugar percentage (table 2, case 3) rather than the fall (table 1, case 3) which occurred under insulin alone. On March 30 he was given an intravenous sugar tolerance test with the result recorded on chart 1, case 1. During the first three weeks in April there was only an occasional trace of sugar in his urine, but his blood sugar on repeated tests remained slightly elevated, averaging 0.15 per cent.

On April 22, 1926, under ether, the usual transsphenoidal operation was performed with the partial removal of a chromophile adenoma. The procedure, owing to anatomic conditions, was difficult and prolonged and was not as radical as it might otherwise have been.

In spite of this long operation his first postoperative specimen of urine showed no sugar, nor was there any increase in the percentage of blood sugar. On the contrary, his blood sugar showed on successive tests a moderate fall below the previous average of 0.15 per cent. On May 13 he was given his first postoperative intravenous sugar tolerance test (chart 1, case 1) when his fasting blood showed 0.12 per cent, and the curve was considerably lower than his preoperative curve.

From the time of his operation until his discharge on May 17, his urine remained sugar-free. Meanwhile he not only had a marked subjective improvement in his pressure symptoms, but there was a definite objective subsidence in his acromegalic "myxedema." At the present time, six months later, he remains well, and according to reports from the Veterans' Bureau in New York there has been no glycosuria, though the blood sugar when last tested showed 200 mg per one hundred cubic centimeters of blood.

Here, then, was a man retained in the hospital for purposes of study over a long period, who at entrance showed a 5.5 per cent of glycosuria with a total twenty-four hour output of 104 Gm of sugar, and who subsequently became sugar-free even though his hyperglycemia persisted. It can hardly be claimed that the comparatively unsatisfactory operation in this case and the disappearance of his glycosuria were anything more than coincidental, and the case is given largely to show the difficulties of interpretation which attend these studies.

There have been other cases of acromegaly in the series with serious grades of persistent diabetes with which the partial and conservatively conducted hypophysectomy has had no definite effect on the disturbed sugar metabolism. What is more, in one or two of these intractable cases it has been found particularly difficult to get the disorder under even partial control by insulin. Acromegalic patients often have an inordinate appetite even when they are not glycosuric. Their polyphagia often completely dominates them, and since they are not prone to lose weight and often feel more miserable from the effects of their "acromegalism" when their food is restricted, they look on their diabetes as a secondary consideration and treat the admonitions of the physician with indifference.

The following case will illustrate this point and at the same time will show not only that a severe diabetes may be surprisingly well borne by an acromegalic patient but also how relatively intractable it may be to insulin before an operation.

*Acromegalic male with diabetes of six years' duration. Diabetes most recalcitrant to insulin before hypophysectomy, easily controlled subsequently.*

An Indiana farmer, aged 41, was admitted to the hospital on Nov 25, 1925. He showed advanced acromegaly, the changes in his features and extremities having been first noted about ten years previously. Six years before admission, following an attack of influenza, he began to have severe bitemporal headaches, increase in thirst and polyuria. Glycosuria was discovered at that time, and

dietary treatment instituted. He adhered to the restrictions for twenty months, felt well enough meanwhile, but at times the urine showed a good deal of sugar. This so discouraged him that he abandoned the diet and yet in spite of a ravenous appetite which was fully satisfied he continued at times to be sugar-free and at others to show large quantities of sugar. He meanwhile was engaged in heavy manual labor, and for the month before he came under observation had been pitching hay and following a plough.

At the time of admission, aside from the marked acromegalic overgrowth, the primary optic atrophy, typical defects of the visual field, and the large sella turcica demonstrated by roentgen-ray examination, he showed a blood sugar of 0.28 per cent, glycosuria of from 5 to 6 per cent with a daily excretion of from 125 to 150 Gm of sugar. No acetone bodies were at any time detected in the urine.

After a week of preliminary observation he continued to show from 5 to 7 per cent of urine-sugar without ketosis on a full diet. He was then put on a diet restricted only in the sense that bread and sugar were limited, and an insulin regimen averaging 15 units three times a day. His fluid intake and output immediately became reduced from 3,500, 4,000 to around 2,000 cc daily, and his glycosuria to from 1 to 2 per cent, but his blood sugar continued at 0.25 per cent. His basal metabolic rate, which was  $+38$  per cent before the use of insulin, had dropped to  $+14$  per cent after five days' treatment. At the end of this period a return to an unrestricted diet without insulin promptly resulted in an elevation of the glycosuria and fluid-exchange and a rise in the basal metabolic rate to  $+22$  per cent. A week later insulin with dietary restriction was resumed, and it was found that 25 units three times a day for five days did not eliminate his glycosuria, and the amount was carried up to 40 units three times a day without rendering the urine sugar-free. He was operated on the following day.

*Operation—Dec 23, 1925* By the usual transsphenoidal operation under ether anesthesia a generous portion of his pituitary adenoma was removed. He seemed little disturbed by the operative procedure, although his blood sugar taken at the end of the operation had risen to 0.36 per cent. Five hours later it was 0.23 per cent.

He made an uncomplicated recovery from the operation, following which, without insulin and on an unrestricted diet, he showed a marked polyuria and a urinary sugar excretion at times of over 300 Gm, but there were never any signs of acidosis.

On Jan 18, 1926, he was put on a weighed diet of 3,000 calories (carbohydrate 100, protein 125, fat 250) with 30 units of insulin twice daily. He continued, however, to show at least a trace of sugar until his discharge on January 26. The blood sugar had remained in the neighborhood of 0.25 per cent until his last day in the hospital when it had suddenly dropped to 0.13 per cent, and for the first time since his admission his urine failed to show sugar. He has since continued on an insulin regimen of 25 units twice a day, has resumed his active life, and though he shows great variability in his glycosuria, his physician reports his condition to be greatly improved.

What particularly struck Dr. Fitz, who collaborated with us in the conduct of the case, was the fact that a man with diabetes of six years' standing who had largely ignored it for over four years and yielded to the dictates of a ravenous appetite showed no acetone bodies in the urine, and who, in spite of a complaint of weakness, had engaged in heavy labor up to the time of his admission. He responded to insulin by a decrease in sugar output, but his blood sugar remained little affected, and it was not until after his operation that an insulin regimen

in amounts which previously had been ineffective finally caused his glycosuria to disappear and reduced his hyperglycemia. How much if any credit for this may be given to the partial hypophysectomy is difficult to say. Certainly the changes were not immediate nor were they striking. Even so, the hypophysis is not necessarily ruled out as the important factor, for insufficient tissue may have been removed to cause a prompt effect, or the pancreatic islets may have been seriously damaged by his long-standing and neglected diabetes.

Another similarly intractable case in the series in which the diabetes remained unmodified after a possibly insufficient removal of the adenoma has been kindly studied for us by Dr. E. P. Joslin. This patient suffers from intolerable acromegalic headaches and is quite indifferent to her outspoken diabetes of about two years' duration which has been notably resistant to insulin in our hands as well as in the hands of others. In this case also though Dr. Joslin found her melituria to be influenced by insulin, he found also that her blood sugar did not seem to be correspondingly modified but remained surprisingly high when compared with the amount of sugar in the urine. This patient also feels much better when on an unrestricted diet, frets under an insulin regimen, and seems to do just as well without it.

Another point that might be mentioned is that patients with acromegaly and diabetes may nevertheless pass safely through severe infections and serious surgical operations and ultimately succumb to some cause unassociated with the diabetes. There are several examples of this in our series which might be detailed were it not that the literature contains many reports of the kind, and the added recital herein of others would unduly prolong this discussion.

It is undoubtedly true, on the other hand, that many acromegalic patients with diabetes end their days after the expected fashion of patients afflicted with the latter disease alone, that is, by coma supervening on a pneumonia or some other infection. Froment<sup>50</sup> collected twelve examples of this from the literature, one of John's<sup>46</sup> patients met with a similar end, and undoubtedly a record of many others might be found. Thus one of the twelve patients with acromegalic diabetes in the series under review died in coma as recorded in detail in a previous paper,<sup>2</sup> the postmortem examination failing to show any recognizable abnormalities in the pancreas.

It is evident from a comparison of the causes of death of acromegalic patients with diabetes with the causes of death of patients with pancreatic diabetes as cited by Root and Warren<sup>22</sup> from Joslin's clinic that the former are more often unrelated to the disturbance of sugar metabolism. This, after all, is what would be expected in view of the

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<sup>50</sup> Froment, J. Rapport de réunion Société de Neurologie, *Rev. neurol.* 29: 663, 1922.

many added complications which the acromegaly and its tumor would incur. However, in spite of this the average survival period after the appearance of the glycosuria proves to be about the same in both groups, namely, from ten to eleven years,<sup>51</sup> which would indicate a better prognosis for the diabetes of acromegaly considered by itself.

Associated with the acromegalic diabetes, moreover, in many instances is a high basal metabolic rate and this constitutes another point of difference from ordinary diabetes in which, as is well known, the basal metabolic rate is not markedly affected whether the patient is insulinized or not. This we have touched on in a preceding paper dealing with the metabolic rate in the disease.<sup>3</sup> The complexity of the problem therefore, owing to the secondary effects of the hyperpituitarism on the thyroid as well as on the pancreatic islets is undeniably considerable.

#### THE EFFECT OF HYPOPHYSIAL OPERATIONS ON SUGAR TOLERANCE IN ACROMEGALY

The argument has been raised by those who regard diabetes mellitus as the same disease whether or not it is accompanied by acromegaly, that a hypophysectomy has never been known to bring about a cure of the diabetes. This is a matter which perhaps requires some explanation by the surgeon.

It scarcely needs to be emphasized that surgery of the hypophysis in general is still in its infancy, that the operations which are gradually becoming perfected have in the past been almost wholly confined to the single purpose of preserving vision by relieving the chiasm from the effects of pressure by the adenoma, that the adenomas so attacked are far more often accompanied by the clinical aspects of hypopituitarism, a condition the reverse of acromegaly, than by acromegaly itself.

Consequently, operations on acromegalic patients with this primary purpose in view, of lessening the pressure effects of a large adenoma which have at the same time served to lessen the general effects of the hyperpituitarism, have been few. What is more, the number of operations on acromegalic patients with diabetes in which both preoperative and postoperative dependable determinations of blood sugar have been made almost reach the vanishing point.

Hence when one speaks of "curing" the diabetes of acromegaly by a hypophysectomy, we have as yet not much to go on. In dealing with such a complex subject and one with so many facets as the treatment of hyperpituitarism, regardless of its secondary complications, progress comes slowly. The problem is technically far more difficult than the

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<sup>51</sup> In the days before insulin the average survival period of patients with pancreatic diabetes was variously estimated at from four (Fitz and Murphy) to six (Joslin) years.

operative treatment of, for example, hyperthyroidism for which a subtotal thyroidectomy has become a fairly well standardized procedure

Possibly the most convincing case in the literature is that reported by Ellis,<sup>40</sup> to which reference has already been made

A woman, aged 42, with acromegaly of ten years' standing and diabetic symptoms of possibly eight months' duration, showed 0.43 per cent blood sugar and 10 per cent glycosuria with acetone bodies in large quantities. After three days' fasting she became sugar-free and was maintained so by a limited diet for three weeks. Then by a long operative procedure under ether a partial extirpation of the pituitary growth by the transfrontal route was performed. She showed only a trace of glycosuria postoperatively, and in spite of increasing laxity of diet had remained free from glycosuria up to the time of the report three years later, although sugar tolerance tests showed a relative hyperglycemia.

In this case M<sup>1</sup> Walton, the surgeon, from all accounts carried out a more radical extirpation of the hypophysial adenoma than is usually accomplished, though the pathologist's description of the tissues described them as fragmentary. However this may be, the acromegalism so far as the diabetes was an expression of its activity, appears to have been definitely checked for a period of thirty-six months when the case was reported.

In the 100 examples of outspoken acromegaly made the basis of this series of papers, twenty-five of them, as stated, showed various grades of melituria, and of these patients fourteen have been subjected to hypophysial operations usually because of symptoms of tumor and most of them in days gone by without any particularly detailed observations on the degree and course of the existent glycosuria or diabetes. Since our interest in the matter has become revived, we have observed an immediate postoperative cessation of a preexisting glycosuria in only one case, a brief account of which follows.

*Acromegaly of moderate degree. Transsphenoidal operation with radical removal of small adenoma. Immediate cessation of preexisting glycosuria.*

A married Italian woman, 22 years of age, first came under observation on Dec. 17, 1925, with the chief complaint of headaches. These were of two years' standing and had set in during the course of her first and only pregnancy. The headaches during this period had become increasingly severe. Meanwhile her hands and feet had enlarged, her features had become coarse and heavy, a growth of hair had appeared on the lip and chin with general hypertrichosis, and there had been a notable increase in weight. There was marked sweating and nervousness. She had a small sella and no disturbance of vision. There was no glycosuria and the blood sugar showed 0.13 per cent. She was discharged.

She reentered the hospital on Aug. 27, 1926, owing to great increase in her cephalalgia and in her general symptoms of acromegalism. Her urine on admission showed no sugar, but on September 2 she was found to have a glycosuria amounting to 0.7 per cent (9.5 Gm.). Without dietary restrictions the urine continued to hold about this percentage of sugar until the operation. On one occasion, September 6, she showed diacetic acid which may possibly have been due to the acetylsalicylic acid she was taking for her headaches. She

had an increased basal metabolic rate of  $+25$  per cent and was put on Lugol's solution on *September 2*, 5 drops three times a day, which was continued for fourteen days without appreciably affecting the rate. Her blood sugar on *September 10* was 0.14 per cent.

On *September 20, 1926*, under ether anesthesia she was operated on by the usual transsphenoidal route with the purpose of radically cleaning out her adenoma even though she showed no local symptoms other than her severe acromegalic headaches. The operation, which was easily conducted, was satisfactory in all respects, the tissue showed an acidophilic adenoma. She made an excellent recovery with immediate cessation of her headaches and early subsidence of her pituitary myxedema.

Her blood at the termination of the operation on *September 20* showed a sugar content of 0.24 per cent, three days later, on *September 24*, 0.12 per cent, on *September 28*, 0.11 per cent, and on *October 1*, 0.09 per cent.

There was an immediate postoperative disappearance of her glycosuria, not a trace of sugar having been observed at any subsequent examination during her hospital sojourn. She was discharged on *October 20*.

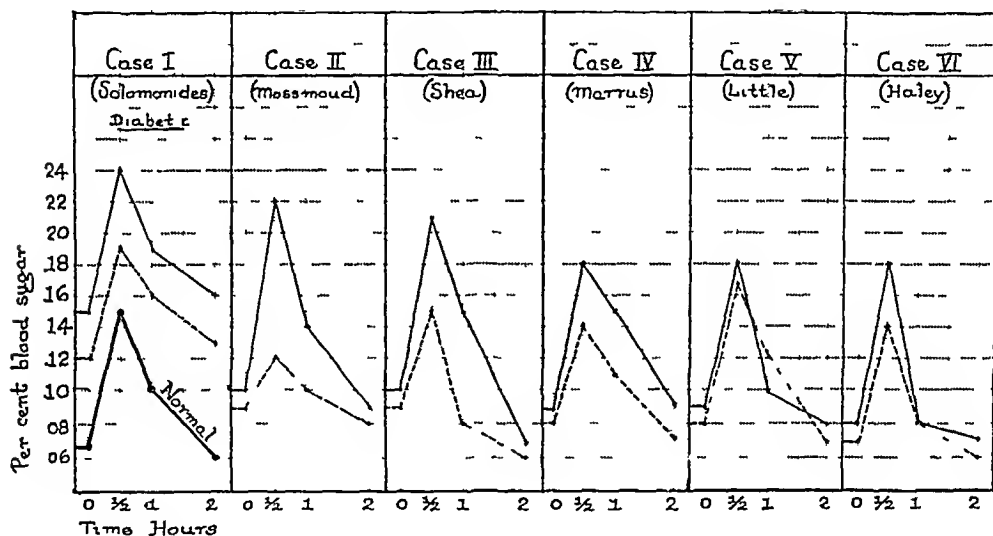


Chart 1—Blood sugar tolerance curves in six cases of acromegaly before (continuous) and after (broken lines) operation, showing a postoperative lowering in the blood sugar levels. The heavy lines represent a normal curve for comparison.

Although such a case as this is suggestive, it can hardly be spoken of as a "cure" of acromegalic diabetes, for when the patient came under observation, there may have been merely a wave of melituria with which the operation happened to coincide. Her postoperative fall in blood sugar, however, is something to which we desire to call especial attention, for it permits us to tell, in closing, another story which is perhaps more convincing. This concerns the effect of the hypophysectomy on the hyperglycemia of acromegalic patients in the absence of any history of glycosuria. The lowering of the existing hyperglycemia by the partial removal of an acromegalic adenoma under these circumstances indicates what may come to be accomplished in the more severe grades of disturbed sugar metabolism when more radical operations are devel-

oped and successfully undertaken. For with the knowledge that hypopituitarism is associated with a relative hypoglycemia and assuming the existence of hyperpituitarism with adenomatous changes in every case of acromegaly, at least during the active stages of the disease, it would seem justifiable to expect an improvement in the patient's impaired carbohydrate tolerance by a partial operative removal of the hyperplastic tissue. In six of the nine patients mentioned in the section on sugar tolerance whose blood was studied both before and after operation, we have observed such a response.

In chart 1 the curves of sugar determinations in these cases are separately shown, those taken before operation in continuous and those

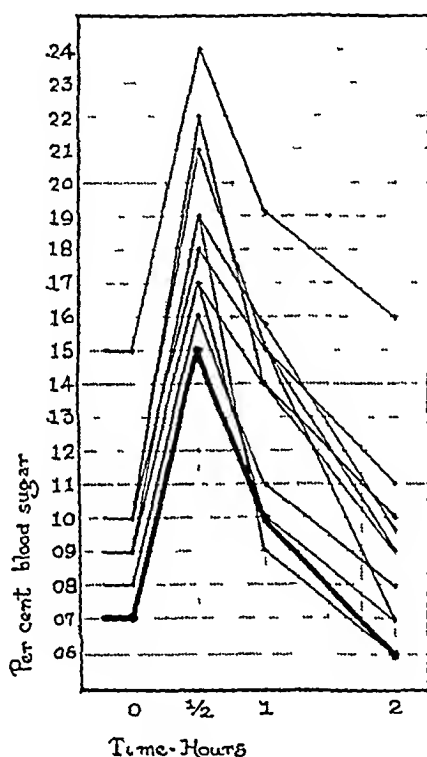


Chart 2—Preoperative blood sugar tolerance curves in six cases, and four curves in three additional cases in which operation was not performed, all superimposed, showing invariable decrease in sugar tolerance. Normal curve in heavy lines is for comparison.

taken after operation in broken lines. It is evident at a glance that in all but two of the cases, in which the changes are insignificant, there has occurred a distinct improvement on the part of each patient to handle glucose after the partial hypophysectomy. In chart 2 are shown the preoperative curves of these and a few other curves of cases in which operation was not performed, all of which have been superimposed and to which reference has been made in the section on "Sugar Tolerance." Chart 3 presents the superimposed postoperative curves of the six cases, and shows the distinct lowering of the blood sugar levels when contrasted with chart 2.

The six patients selected for this study included one with mild clinical diabetes (case 1) whose curve improved strikingly. The others were all typical acromegalic patients without diabetes who had pre-operative tests, and who had varying amounts of their chromophile adenomas removed at operation. It is of significance that the patient (case 2) in whom the improvement in the sugar tolerance was most marked had the most radical operation of the entire group, also that the patients whose postoperative increase in tolerance was least marked had the least amount of tissue removed at operation.

In addition to the increase in sugar tolerance, moreover, these patients all showed a distinct improvement in the outward manifestations of

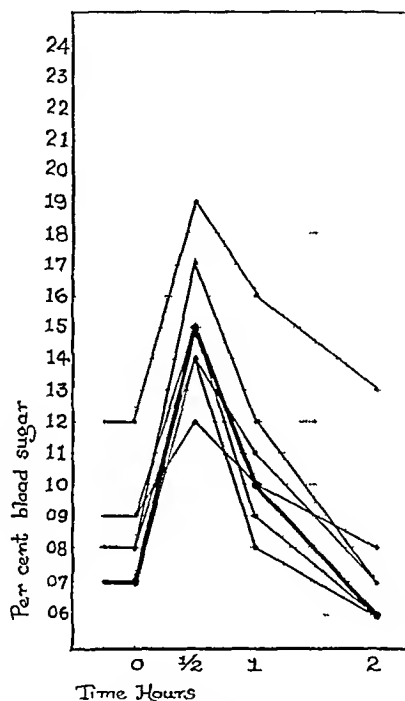


Chart 3—Postoperative blood sugar tolerance curves in six cases included in chart 2, showing distinct lowering in sugar levels (Increase in sugar tolerance)

their acromegaly, such for example as a decrease in the size of the hands and feet owing to the disappearance of the peculiar thickening of the soft parts so characteristic of active acromegaly. Still another concomitant change has been the lowering of the basal metabolic rate following operation, which we have been led to interpret as a manifestation of reduction in pituitary activity.<sup>3</sup>

We may therefore deduce from these observations (1) that the function of metabolizing carbohydrates is frequently impaired in acromegaly, amounting in many cases to actual clinical diabetes mellitus, and (2) that measures taken to reduce the hyperactivity of the pituitary anterior lobe seem to have a beneficial effect on the patients' ability to handle sugars.

Whether these findings indicate that the hypophysis may directly influence the capacity of the body to utilize carbohydrates, or whether the effect occurs only through some secondary disturbance of the glycolytic function of the pancreatic islets, there is as yet no positive way of determining. We are inclined to favor the latter view, but in either case the hypophysis so far as we can see plays the leading rôle.

In H. M. Evans' Harvey Lecture for 1924 on "The Function of the Anterior Hypophysis" he states

The hypophysis stands in a necessary relationship to the normal function of the thyroid, sex glands and adrenal cortical tissue. Any explanation of how these effects are mediated constitutes part of the ill-understood field of chemical dependencies and correlation within the body, ignorance of which cannot properly place in doubt evidence that correlation exists.

To these three subsidiary endocrine organs that Dr. Evans mentions, of whose activity the hypophysis is a regulator, we may definitely add the pancreatic islets, and may further state that in hyperpituitarism (acromegaly) the inter-reaction so far as the thyroid (and possibly the parathyroid) and suprarenal cortex are concerned is an acceleration of function. It is possible that this may also be true of the pancreatic islets and of the sex glands as well, even though symptomatically they show respectively the amenorrhea and relative hyperglycemia commonly interpreted as evidences of lowered function. The amenorrhea, however, as Evans has shown, may be otherwise explained, and the hyperglycemia may merely be an indication of temporary exhaustion of the islets from overstimulation and thus represent a condition from which recovery is possible.

#### SUMMARY AND CONCLUSIONS

It is coming to be the consensus of opinion of those who have concerned themselves with the subject, that acromegaly represents a state of hyperpituitarism which is ascribable to the overaction of the acidophilic cells of the pars anterior. With this opinion our studies as presented in previous numbers of this series are in full agreement.

It has been emphasized in a paper dealing with the findings in four autopsied cases that hyperpituitarism as represented by acromegaly stands apart from other endocrine disorders in its striking secondary effects on the other ductless glands, notably in an adenomatous hyperplasia of the thyroid, in an hypertrophy or adenomatosis of the suprarenal cortex, and in adenomatous changes in the parathyroids.

In addition to these hypertrophic changes, a diminished functional activity affects the gonads and similarly there appears to be diminished power of metabolizing carbohydrates which is generally assumed to be the sole function of the pancreatic islets.

In a discussion of the increased basal metabolic rate seen in the disease the stand was taken that this was primarily a hypophysial disturbance even though the thyroid without doubt was secondarily affected. The substantiation for this view was the definite lowering of the metabolic rate following partial extirpations of hypophysial adenomas.

There are ample reasons to support the belief that the meliturias which occur in about 25 per cent of all cases of acromegaly may be similarly accounted for as primarily hypophysial, even though the pancreatic islets doubtless play a secondary rôle in their production. To be sure, the diabetes of acromegaly responds to insulin just as the increased basal metabolic rate of acromegaly responds to Lugol's solution. But neither of these responses appear to be quite so definite as are the responses in primary pancreatic diabetes to insulin and in primary exophthalmic goiter to Lugol's solution.

We may conclude that the glycosurias which accompany acromegaly are ascribable primarily to the hyperpituitarism for the following reasons:

- 1 Patients with acromegaly (hyperpituitarism) even in the absence of spontaneous glycosuria usually have a low sugar tolerance and tend to show some measure of hyperglycemia, whereas patients with the reverse condition (hypopituitarism) usually have a high tolerance for sugars and ordinarily show definite hypoglycemia.

- 2 Though the melituria of acromegaly may terminate as ordinary diabetes does in a state of coma, the condition nevertheless shows marked variability in its degree of intensity and appears to be spontaneously recoverable, which is seldom if ever true of primarily pancreatic diabetes.

- 3 Insulin and posterior lobe extracts have been shown to be, and insulin and active anterior lobe extracts may be presumed to be, counteractive in their effects. Whether in acromegaly the melituria is due to an excess of posterior lobe extract, as the counter-effects on insulin would appear experimentally to indicate, or to an overactivity of the acidophilic cells of the anterior lobe as we are inclined to believe, or possibly to a combination of both, for we know little of the source of the active substance of the posterior lobe, time will surely tell. Hyperpituitarism in any case produces a substance which enters the circulation and counteracts the normal functional activity of the pancreatic islets, glycosuria being the frequent consequence.

- 4 Insulin will control acromegalic diabetes, but far less effectively than it does the more common forms of diabetes unassociated with hyperpituitarism, the assumption being that the increased pituitary activity tends to counteract its effects.

5 The partial extirpation of the acromegalic adenoma by surgical procedures will apparently render patients with diabetes more amenable to insulin and may promptly lower the tendency to hyperglycemia exhibited by many of these patients even in the absence of active glycosuria. It may be anticipated that more radical procedures than those customarily undertaken, now that the operation has become reasonably safeguarded and perfected, will similarly serve to reduce the hyperpituitarism to such a degree as to check effectually and permanently actual acromegalic glycosuria or possibly even acromegalic diabetes.

# THE INFLUENCE OF MENSTRUATION ON THE CONCENTRATION OF CALCIUM IN BLOOD PLASMA \*

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Over thirty-five years ago Fehling<sup>1</sup> showed a relationship between ovarian function and calcium metabolism by demonstrating the curative action of oophorectomy on osteomalacia following pregnancy. With the development in recent years of satisfactory microchemical methods for the estimation of the inorganic constituents in blood, calcium has been receiving ceaseless attention with a view to establishing the manner of its manifold operation in the animal economy. Among the many such studies, some have been directed toward investigations of the influence of the menstrual cycle on the concentration of calcium in blood.

We do not propose herein to discuss the literature pertinent to this topic, nor to undertake the recital of the many theories offered by investigators in explanation of their varied observations. The present status of the conclusions in this problem may be accepted as indicated in three recent publications, those by Rittmann,<sup>2</sup> Schultze<sup>3</sup> and Heyn and Haase<sup>4</sup>. From these one infers that while the menstrual cycle does influence the level of the blood calcium, such an influence is not always in the same direction nor operative in all women to the same degree. A distinct weakness is present in all the studies thus far reported in that in the effort to demonstrate the extent and manner of the cyclic influence of menstruation no attempt has been made to secure a series of consecutive specimens of blood from the same subject. Such data are presented in this article.

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1 Fehling, H. Ueber Wesen und Behandlung der Puerperalen Osteomalakie, Arch f Gynak **39** 171, 1891

2 Rittmann, R. Blutcalcium Spiegel und Menstruation, Wein Arch f inn Med **8** 261 (July) 1924

3 Schultze, G K F. Ovarialtatigkeit, Kalium-Calcium Gehalt des Blutserums und Vegetatives System, Arch f Gynak **126** 35 (Jan) 1924-1925

4 Heyn, A, and Haase, K. Ueber die Beziehungen der Ovarialfunktion zum kalkgehalt des Blutserums, Arch f Gynak **126** 646, 924-1925

## METHOD

The subjects studied were three women who menstruated regularly and who, aside from the usual accompanying physiologic unrest, were in no way inconvenienced by it. They were requested to record the dates of the onset and course of each menstruation, as well as the time and character of the symptoms observed. The interval between successive menstruations usually being a multiple of seven days, we endeavored to take specimens of blood every six days, thus hoping to vary continually the time relationship of the specimen of blood to the first day of menstruation. These specimens were taken before breakfast a minimum amount of citrate being used as an anticoagulant.

Plasma calcium,<sup>5</sup> chlorine on whole blood and corpuscular volume were estimated in each specimen. Chlorine was determined in order to supply values on an ion whose variations were, as far as is known independent of the influences we were studying, thus affording a further basis for interpretation of the variations in the cation calcium. Records on the corpuscular volume served to disclose the influence of hydremia or its opposite when operative on the concentration of calcium which is confined chiefly to the plasma.

A study of the protocols given by our three subjects indicated that those symptoms in each instance referable to what we have called the physiologic unrest accompanying menstruation anticipated the onset of menstruation by from several days to a week, and maintained themselves in one form or another throughout the menstrual period and even beyond. Although we may appreciate that in introspective analysis of this kind overzealous subjects may tend to overestimate the time factor in the effects recorded, it seems fair to accept for purposes of interpretation of our data a division of the twenty-eight to thirty day cycle into a menstrual half, covering the seven to eight days preceding and succeeding the date of onset of flow, and an intermenstrual half, covering the remaining days of the cycle.

Subject 1 was a laboratory technician, aged 36, German, blond, unmarried, 5 feet and 1 inch in height, weighing 105 pounds (47.6 Kg).

Subject 2 was a nurse, aged 31, American, brunette, married nine years, and had had one pregnancy. She was 5 feet and 3 inches in

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<sup>5</sup> Kramer, B., and Tisdall, F. E. A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, *J Biol Chem.* **47** 475 (Aug) 1921. Whitehorn, J. C. Simplified Method for the Determination of Chlorides in Blood or Plasma, *J Biol Chem* **45** 449 (Feb) 1921. (Chlorine was estimated on whole blood, this is compulsory for securing acceptable values when no attempt is made to control the interchange of chlorine between corpuscles and plasma as influenced by the partial carbon dioxide pressure of laboratory environment.)

height, and weighed 175 pounds (79.4 Kg) She was distinctly obese and plethoric

Subject 3 was a nurse, aged 33, American, blonde, 5 feet and 10 inches in height, weighing 126 pounds (57.2 Kg) She was conspicuously long-boned

In tables 1, 2 and 3 are contained the analytic data on the specimens of blood of these three subjects A study of these data indicates, first, that the concentrations of calcium are independent of plasma corpuscle ratios, second, that no correlation exists between the variations in measures of chlorine and calcium, and third, that the highest concentrations of calcium seem distinctly to be confined to those days of the twenty-eight to thirty day cycle defined in the foregoing as the menstrual half

In table 4 the data concerning the chlorine and calcium content of the blood are expressed as percentages of the lowest figure in each series, this at once demonstrates that the variations in chlorine and calcium are independent and of a different order

In table 5 the data concerning the chlorine and calcium content of the blood of each subject are segregated in two groups, those belonging to the menstrual and those belonging to the intermenstrual periods as defined in the foregoing It further emphasizes the variations of chlorine concentration as independent of the menstrual cycle and shows the consistent tendency of the blood calcium to maintain itself at a higher concentration during the menstrual half of the month

#### COMMENT ON AND DETAILED ANALYSIS OF DATA

Duplicate estimates of calcium on specimens of blood gave values that differed by less than 0.15 mg per hundred cubic centimeters Five times this amount (0.75 mg per hundred cubic centimeters) may safely be accepted as indicative of a significant change in concentration

SUBJECT 1—The first recorded menstrual days, April 30 to May 2 inclusive (three days), reflected no influence on the concentration of calcium Unfortunately, however, the two specimens of blood taken nearest these dates covered the third day before the onset and one day after the completion of flow, and, under the circumstances, a significant influence on the concentration of calcium might have occurred during the six day interval between the days when these two specimens of blood were taken On May 26, two days before the next menstrual flow, the blood increased 1.25 mg over that of the preceding specimen, reaching 10.79 mg, and maintained this level through June 1, the last of a five day flow On June 22, the first day of flow of the third menstrual period, the blood again showed a significantly high calcium content (10.22 mg), a rise of 1.29 mg over the preceding specimen

TABLE 1—Corpuscular Volume, Whole Blood Chlorine and Plasma Calcium as Estimated in Subject 1

Date	Corpuscular, per Cent by Volume	Whole Blood Chlorine as Sodium Chloride, Mg per 100 Ce	Plasma Calcium, Mg per 100 Ce
4/15/26			9.92
4/21/26			9.44
4/27/26	40.0	532	9.22
4/30/26 (first day of menstruation)			
5/ 2/26 (last day of menstruation)			
5/ 3/26	39.3	554	9.26
5/ 8/26	38.0	499	9.22
5/14/26	39.4	490	9.36
5/20/26	39.1	499	9.51
5/26/26	38.5	474	10.79
5/28/26 (first day of menstruation)	40.8	499	10.89
6/ 1/26 (last day of menstruation)	45.0	495	10.94
6/ 7/26	40.1	482	9.52
6/12/26	36.4	490	8.71
6/18/26	40.0	507	8.93
6/22/26 (first day of menstruation)	38.4		10.22
6/24/26	45.1	515	9.95
6/26/26 (last day of menstruation)			
6/30/26	40.6	482	9.44

TABLE 2—Corpuscular Volume, Whole Blood Chlorine and Plasma Calcium as Estimated in Subject 2

Date	Corpuscular, per Cent by Volume	Whole Blood Chlorine as Sodium Chloride, Mg per 100 Ce	Plasma Calcium, Mg per 100 Ce
4/12/26			8.99
4/19/26			8.90
4/24/26			8.99
4/30/26	46.1		9.06
5/ 1/26 (first day of menstruation)			
5/ 5/26 (last day of menstruation)			
5/ 7/26		482	9.40
5/13/26	41.7	482	9.36
5/20/26	41.8	485	9.27
5/26/26	40.5	482	9.17
6/ 2/26 (first day of menstruation)	42.6	465	10.60
6/ 5/26 (last day of menstruation)			
6/ 8/26	43.6	482	9.04
6/15/26	48.1	492	8.98
6/21/26 (appearance of menstrual symptom, enlargement of breasts)			
6/23/26	41.7		10.13
6/30/26	48.3	474	8.91
7/ 1/26 (first day of menstruation)			

TABLE 3—Corpuscular Volume, Whole Blood Chlorine and Plasma Calcium as Estimated in Subject 3

Date	Corpuscular, per Cent by Volume	Whole Blood Chlorine as Sodium Chloride, Mg per 100 Ce	Plasma Calcium, Mg per 100 Ce
4/20/26 (first day of menstruation)			9.67
4/26/26 (last day of menstruation)			9.56
5/ 1/26	47.8	561	9.06
5/ 7/26	40.0	569	9.33
5/13/26	38.0		11.32
5/15/26 (first day of menstruation)	39.5	507	
5/19/26			9.60
5/21/26 (last day of menstruation)	35.5	565	
5/25/26	35.2	532	9.36
6/ 1/26	45.0	515	9.55
6/ 7/26	41.7	532	9.39
6/11/26 (first day of menstruation)			
6/12/26	39.6	540	9.15
6/18/26 (last day of menstruation)	40.6	533	8.88
6/24/26	39.0	490	9.04
6/30/26	41.7	524	9.07

TABLE 4—*Chloride and Calcium Expressed as a Percentage of the Lowest Measure in the Series for Each Subject Respectively*

Subject 1		Subject 2		Subject 3	
Calcium	Chloride	Calcium	Chloride	Calcium	Chloride
114		101		109	
108		100		108	114
106	112	101		102	116
106	117	102		105	
106	105	107	104	128	104
107	103	105	104	108	115
110	105	103	105	105	109
124	100	104	104	108	105
125	105	119	100	106	109
126	104	102	104	103	110
110	102	101	106	100	109
100	103	113		102	100
114	107	100	102	102	107
118					
114	109				
108	102				

TABLE 5—*Values for Chloride and Calcium (Mg per One Hundred Cubic Centimeters Blood) Arranged According to Menstrual and Intermenstrual Grouping (See Text)*

	Menstrual		Intermenstrual	
	Calcium	Chloride	Calcium	Chloride
Subject 1	9 22	532	9 92	
	9 26	551	9 44	
	10 79	474	9 22	499
	10 89	499	9 36	490
	10 94	495	9 54	499
	8 93	507	9 52	482
	10 22		8 71	490
	9 95	515		
	9 44	482		
Average	9 96	507	9 39	492
Subject 2	9 06		8 99	
	9 49	482	8 90	
	9 17	482	8 99	
	10 60	465	9 36	482
	9 04	482	9 27	485
	10 13		8 98	492
	8 91	474		
Average	9 49	477	9 08	486
Subject 3	9 67		9 06	569
	9 56	561	9 33	
	11 32	507	9 36	532
	9 60	565	9 55	515
	9 39	532	9 04	490
	9 15	540		
	8 88	533	9 07	524
Average	9 65	540	9 24	526
Average all subjects	9 72	509	9 23	504

Forty-eight hours later, and still during the menstrual flow, this high level was maintained. The records in this case are suggestive of the inference that the concentration of calcium in the blood rises shortly before the menstrual flow and drops again after it.

**SUBJECT 2**—In this subject's records only two significant rises in the concentration of calcium appeared. On June 2, the first day of menstrual flow, a rise of 1.43 mg over that of the preceding record occurred, disappearing in the next specimen taken two days after a five day flow. The second significant rise, June 23, 1.15 mg over the concentration of the preceding sample, occurred eight days before the onset of the menstrual flow but forty-eight hours after the appearance of a menstrual symptom (engorgement of the breasts). The last record of this series, taken twenty-four hours before the first day of flow, showed a drop to the normal level. The relationship of high blood calcium to the menstrual period is not convincingly brought out in this case, still, the two recorded rises not only are within the fourteen days ascribed to the menstrual half of the cycle, but are also definitely related in the one case to the onset of flow, and in the other to the appearance of the physiologic unrest accompanying menstruation.

**SUBJECT 3**—In this subject there is one record on the first day of flow and another forty-eight hours before the onset of flow. These are the two highest concentrations in the series, 9.67 mg (April 20) and 11.32 mg (May 13). Of these two, only the latter can be accepted as appreciably high. No menstrual influence is discernible in the concentration of calcium for the last recorded menstrual cycle, June 11 to June 18, but, if in this subject we were dealing with a premenstrual elevation of calcium that quickly dissipated itself within the first day or so of flow, all trace of a menstrual influence might be lost in the specimens of June 7 and 12.

In 1908, Blair Bell,<sup>6</sup> determining the calcium content by the crude procedure of counting, in a hemocytometer, the crystals of calcium oxalate precipitated on the addition of oxalate to the blood, reported a sudden rise in blood calcium just before menstruation and presented the hypothesis that this change in the blood picture touched off, so to speak, the rhythmic function of uterine bleeding. He carried the matter further by ascribing to the uterus the function of a calcium-secreting organ, thereby indicating it as the mammalian analogue to the avian calcium-secreting gland. Riddle<sup>7</sup> has recently demonstrated the tremendous increases in calcium in the blood of birds in anticipation of ovulation.

<sup>6</sup> Bell, Blair. Menstruation and Its Relationship to the Calcium Metabolism, *Proc Roy Soc Med* **1** 291, 1907-1908.

<sup>7</sup> Riddle, O., and Reinhart, Warren, H. Studies on the Physiology of Reproduction in Birds. Blood Calcium Changes in the Reproductive Cycle, *Am J Physiol* **76** 660 (May) 1926.

In attempting an interpretation of such data as we here present, at least two glands of internal secretion must be taken into consideration, the ovary and parathyroid—the one with unquestioned influence on menstruation and the other of equally certain influence on the concentration of calcium in the blood. We refer the reader to Corner's<sup>8</sup> excellent review for a summary of the physiologic researches covering pertinent features of ovarian function (ovulation, oestrus and menstruation). Our knowledge of parathyroid activity in conjunction with that of the gonads is yet too meager to merit discussion.

#### CONCLUSION

Although our data have failed to produce with convincing rhythmicity a rise in the concentration of calcium in the blood at the approach and onset of menstruation, they present strong evidence that such a rise probably occurs. This evidence is as strong, possibly, as one could hope for in the presence of the many other concomitant uncontrolled arrhythmic influences operative on blood calcium.

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<sup>8</sup> Corner, George W. Oestrus, Ovulation and Menstruation, *Physiol Rev* **3** 457 (Oct.) 1923.

# THE PROTEIN TEST FOR UREA FORMATION FUNCTION OF THE LIVER

## PRELIMINARY REPORT

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The multiple diverse functions of the liver have given rise to correspondingly numerous and diverse tests for these functions. These tests have been reviewed recently by several authors<sup>1</sup> and evaluated in cases of clinical disease and in experimentally produced hypofunction of the liver. In spite of the fact that one of the most important functions of the liver is the deamination of amino-acids and their conversion to urea—a phase of the physiology of the liver which during the past few years has received much attention and investigation—a standard test for the conversion of urea by the liver has not been elaborated. The hepatic metabolism of carbohydrates,<sup>2</sup> dye elimination,<sup>3</sup> pigment metabolism,<sup>4</sup> detoxifying powers<sup>5</sup> excretion of urobilin<sup>6</sup> and its other func-

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<sup>1</sup> From the Pediatric Service of Mount Sinai Hospital, New York

1 Bauman, Louis. The Physiological and Pathological Chemistry of the Liver, Endocrinology and Metabolism, New York, D Appleton & Co, 1922, vol 4 p 643. Greene, C H, Snell, A M, and Walters, Waltman. Diseases of the Liver. I Survey of Tests for Hepatic Function, Arch Int Med **36** 248 (Aug) 1925. Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, ibid **36** 274 (Aug) 1925. Mann, Frank C, and Bollman, Jesse L. Liver Function Tests, Arch Path **1** 681 (May) 1926.

2 Bauman, Louis (footnote 1). Green, C H, Snell, A M, and Walters, Waltman (footnote 1). McLean, H, and de Wesselow, C L V. The Estimation of Sugar Tolerance, Quart J Med **14** 103, 1920.

3 Rosenthal, S M. An Improved Method for Using Phenoltetrachlorophthalein as Liver Function Test, J Pharmacol & Exper Therap **19** 385, 1922. Rosenthal, S M, and White, E C. Clinical Application of Bromsulphalein Test for Hepatic Function, J A M A **84** 1112 (April 11) 1925. Kerr, W J; Delprat, G D, Epstein, N N, and Dunievits, Max. The Rose Bengal Test for Liver Function, Studies on the Rate of Elimination from the Circulation in Man, J A M A **85** 942 (Sept 26) 1925.

4 Van den Bergh, A. A H. La recherche de la bilirubine dans le plasma sanguin par la methode de la reaction diazoique, Presse med **29** 441, 1921. McNee, J W. Jaundice Review of the Recent Work, Quart J Med **16** 390, 420 (July) 1923. Andrews, C H. The van den Bergh Test in Jaundice, Quart J Med **18** 69, 19 (Oct) 1924. Bernheim, A R. The Icterus Index (The Quantitative Estimation of Bilirubinemia), Its Aid in Diagnosis and Prognosis, J A M A **82** 291 (Jan 26) 1922.

5 Pelkan, K F, and Whipple, G H. Studies of Liver Function. III. Phenol Conjugation as Influenced by Liver Injury and Insufficiency, J Biol Chem **1** 513, 1922. Delprat, G D, and Whipple, G H. Studies of Liver Function. Benzoate Administration and Hippuric Acid Synthesis, J Biol Chem **49** 229, 1921.

tions, including its rôle in ammonia formation,<sup>7</sup> have been the physiologic bases of corresponding tests,<sup>1</sup> but the function of urea formation has largely been neglected

From 1911 to 1917, Van Slyke,<sup>8</sup> with various collaborators, studied the relation of the liver to the metabolism of proteins. He determined the curve of blood urea after a good sized meal of meat.<sup>9</sup> It was also found that the blood urea rose almost at the minute the first particle of food entered the duodenum, as shown by roentgenograms.<sup>9</sup> This point has been corroborated recently by Morgulis<sup>10</sup> through simultaneous determinations of the blood amino-acids and the blood urea after a protein meal, the urea increasing before the amino-acid content of the blood did, or, in other words, before the food was absorbed from the intestine. Mann and his co-workers<sup>11</sup> of the Mayo Clinic have shown, by extirpation of the liver, that urea formation ceases in the absence of the liver. The urea of the blood and tissues decrease rapidly so that only minimum amounts of urea are present twelve hours after total removal of the liver. Coincident with the cessation of urea formation, amino-acids accumulate in the blood and tissues, but not in proportion to the decrease of urea. The fact that muscles readily absorb amino-acids may explain this discrepancy. Through the medium of an Eck's fistula, Mann and his associates then tested the urea formation function of dogs deprived of most of their hepatic tissue or suffering from injury of the liver. Milk and meat were fed in abundance. Their method was to determine the

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6 Elman, R., and McMaster, P. D. Studies on Urobilin Physiology and Pathology. I. The Quantitative Determination of Urobilin, *J. Exper. Med.* **41** 503 (April) 1925. II. Derivation of Urobilin, *ibid.* **41** 513, 719 (June) 1925. *ibid.* **42** 99 (July) 1925, *ibid.* **42** 619 (Nov.) 1925. Wallace, G. B., and Diamond, J. S. The Significance of Urobilin in the Urine as a Test for Liver Function, *Arch. Int. Med.* **35** 698 (June) 1925. McMaster, P. D., and Elman, R. Studies on Urobilin Physiology and Pathology. VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, *J. Exper. Med.* **43** 753 (June) 1926.

7 Burchi, R. Blood Ammonia as a Gage of Liver Function. *Folia Clin. Chim. et Micro.* Milan 1-3, 1926, abstr., *J. A. M. A.* **87** 8 (Aug. 21) 1926.

8 Van Slyke, D. D., and Meyer, G. M. The Amino Acid Nitrogen of the Blood, Preliminary Experiments on Protein Assimilation, *J. Biol. Chem.* **12** 399, 1912-1913, The Fate of Protein Digestive Products in the Body. III. The Absorption of Amino-Acids from the Blood by the Tissues, *J. Biol. Chem.* **16** 197, 1913-1914, The Fate of Protein Digestion Products in the Body. The Locus of Chemical Transformation of Absorbed Amino-Acids, *J. Biol. Chem.* **16** 213, 1913, The Locus of Chemical Transformation of Absorbed Amino-Acids, *J. Biol. Chem.* **16** 213, 1913-1914. Van Slyke, D. D., McLean, F. C., and Cullen, G. E. The Formation of Urea in the Liver, *Proc. Soc. Exper. Biol. & Med.* **12** 93, 1915. Van Slyke, D. D. The Chemistry of the Proteins and Their Relation to Disease, *Oxford Med.* **1** 258, 1920.

9 Van Slyke, D. D., McLean, F. C., and Cullen, G. E. (footnote 8).

10 Morgulis, S. Blood Changes During Digestion with Special Reference to Urea Formation, *J. Biol. Chem.* **66** 353 (Dec.) 1925.

11 Bollman, J. L., Mann, F. C., and Magath, T. B. Studies on the Physiology of the Liver. VIII. Effect of Total Removal of the Liver on the Formation of Urea, *Am. J. Physiol.* **69** 371, 1924.

urea excreted in the urine in twenty-four hours, and definite though slight diminution of the excretion of urea was found. Leucine and tyrosine were absent from the urine in animals from which the livers had been removed completely, showing that the presence of these amino-acids in acute yellow atrophy is probably caused by necrosis of the liver and not by the excretion of an excess in the blood.

From clinicochemical studies it has long been known that in disease of the liver abnormalities in the intermediary metabolism of proteins occur,<sup>12</sup> analogous for the most part, to changes described by Mann and his associates in their studies in total hepatectomy. In acute yellow atrophy and phosphorus poisoning<sup>13</sup> there is an increase in the amino-acids of the blood and a decrease in the blood urea, while the urine is low in urea content and high in ammonia and amino nitrogen. The liver has evidently lost part of its ability to deaminize and to convert amino-acids to urea. The administration of amino-acids to patients suffering from marked disease of the liver is followed by an increased excretion of amino nitrogen in the urine.<sup>14</sup> Urea is decreased in the urine of patients with eclampsia<sup>15</sup> when the predominant pathologic change is a degeneration of the liver. Since all tissues, especially muscles,<sup>16</sup> absorb amino-acids, it is not surprising that mild or moderate instances of disease of the liver do not reveal an increase of amino-acids in the blood.

Most of the present tests for liver function are not without equivocation. For instance, changes in glucose, galactose, or levulose tests may be caused by pancreatic disease as well as by disease of the liver.<sup>17</sup> Increase of the bilirubin of the blood or urobilin of the urine may be caused by increased blood destruction as well as by disease of the liver.<sup>18</sup>

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12 Tileston, W., and Comfort, C. W. The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Method, *Arch Int Med* **14** 620 (Nov.) 1924. Chesney, A. M., and Marshall, E. K., and Rowntree, L. G. Studies in Liver Function, *J. A. M. A.* **63** 1533 (Oct. 31) 1914.

13 Bauman, Louis (footnote 1). Van Slyke and Others (footnote 8). Stadie, W. C., and Van Slyke, D. D. The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver. *Endocrinology and Metabolism, Arch Int Med* **25** 693 (June) 1920.

14 Bauman, Louis (footnote 1).

15 Bauman, Louis (footnote 1). Van Slyke, D. D., and Losee, J. R. The Toxemia of Pregnancy, *Am J M Sc* **153** 94, 1917.

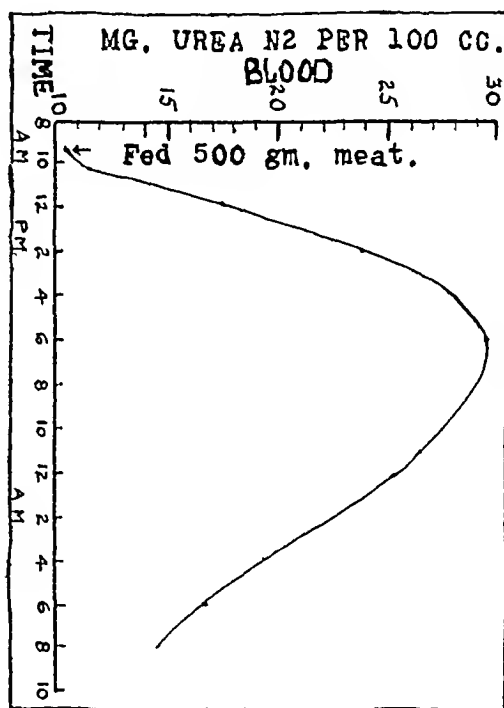
16 Van Slyke, D. D., and Meyer, G. M. The Fate of Protein Digestive Products in the Body. III. The Absorption of Amino-Acids from the Blood by the Tissues, *J Biol Chem* **16** 197, 1913-1914.

17 Joslin, E. P. The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 289.

18 Van den Bergh, McNee and Andrews (footnote 4). Elman, R., and McMaster, P. H. Studies on Urobilin Physiology and Pathology. I. The Quantitative Determination of Urobilin, *J Exper Med* **41** 503 (April) 1925, II. Derivation of Urobilin, *ibid* **41** 513, 719 (June) 1925, *ibid* **42** 99 (July) 1925, *ibid* **42** 619 (Nov.) 1925.

Dyes may be eliminated or absorbed by organs and tissues other than the liver,<sup>19</sup> but the recent work of Mann and his co-workers has shown that the liver is the only organ that has noticeable ability to deaminate and to form urea<sup>11</sup> Hence there is a potential test that is beyond dispute

In disease of the liver the determination of the amino-acids, the ammonia of the blood or the urinary amino nitrogen is a complex task, it is not a perfect test for the reason previously given, namely, that tissues absorb amino-acids The estimation of the urea excreted in twenty-four hours after a heavy meal of meat or milk is not a delicate criterion, for time is allowed for readjustments and compensations, and thus a lag in excretion may readily be overlooked



Time curve of changes in the blood urea during protein digestion (After Van Slyke, *Oxford Med* 1 264, 1920)

As stated before, Van Slyke<sup>20</sup> found a typical curve of blood urea after a protein meal which is reproduced in the chart It will be noted that in four hours the blood urea is about doubled, and in eight hours it is about trebled, after a meal of approximately 15 Gm of protein per kilogram Apparently this was a proper basis for protein tests for liver function Since we were dealing with children, and sick or convalescent children as a rule, we did not think it expedient to take frequent specimens of blood Accordingly, we experimented until we

19 Rosenthal, S M, and White, E C (footnote 3)

20 Van Slyke, D D, McLean, F C, and Cullen, S E (footnote 8)  
Van Slyke, D D (footnote 8)

found that four hours after the protein meal was the most satisfactory time to take the second specimen of blood in children. At this time we could detect the earliest appreciable rise, thereby discovering any lag akin to the glucose tolerance test. Six and eight hour intervals only showed further rise or a continued low blood urea and compensatory rises. We also found it impracticable to feed a child more than 1 Gm of protein per kilogram, which is usually preferred in the form of chicken, the white part being the portion of choice because of its low fat content, but the dark meat may be given if the child prefers it.

#### AUTHOR'S METHOD OF PERFORMING TESTS FOR LIVER FUNCTION

For the purposes of this study, cases of obvious liver injury were selected, but we also investigated cases in which there was reason to suspect disturbed function of the liver. To check our results, other proved and accepted tests for liver function were employed at the same time. The figures of accepted results of these tests were used as standard.<sup>21</sup> A series of control cases with apparently normal function of the liver was studied. After trying various methods, our final procedure was as follows:

1 While the patient was fasting a specimen of blood was taken for (a) blood sugar, (b) blood urea, (c) quantitative determination for bilirubin (the van den Bergh test), and (d) use as standard for dye test.

2 Dye was then injected intravenously. At first the phenoltetrachlorophthalein dye was used, but later we used bromsulphalein because venous thrombosis was frequently caused by the first dye, and because of possible deleterious results like those reported in the literature.<sup>22</sup>

3 Blood was withdrawn for determination of the dye in fifteen minutes and in one hour for the phenoltetrachlorophthalein test or in thirty minutes for the bromsulphalein test.

4 Levulose was given, 15 Gm per kilogram. The blood sugar was then determined every half hour for two or three hours.

5 The protein meal was given, 1 Gm per kilogram, and the blood urea taken four hours later.

6 Twenty-four hour urinalyses were made to determine the amount of urobilin. At first we used the Wallace-Diamond test,<sup>23</sup> but later we employed the more satisfactory Joyce test as modified by Kuttner.

In this way all our tests could be performed in one day, and thus easily repeated when changes in the clinical condition occurred. Checks showed that the tests so performed did not interfere with the results.

As a control series we used children who were suffering from a disease that we were clinically certain did not affect the function of the liver. The effect of a protein meal on the blood urea was studied at two and four hour intervals after the ingestion of the meal, and occasionally six hour studies were made. The results of these tests are shown in table 1.

From the figures in table 1 it will be observed that a two hour interval between the protein meal and the determinations for blood

21 McLean, H, and de Wesselow, C L V (footnote 2) Rosenthal, S M (footnote 3) Rosenthal, S M, and White, E C (footnote 3) Van den Bergh, A A H (footnote 4) Wallace, G B, and Diamond, J S (footnote 6)

22 Rosenthal, S M, and White, E C (footnote 3) Rosemau, W H Dangers in the Use of Certain Halogenated Pthaleins as Functional Tests, J A M A 85 2017 (Dec 26) 1925

23 Wallace, G B, and Diamond, J S (footnote 6)

urea produced an inconstant rise which was not nearly so satisfactory as a four hour interval when the increase of the blood urea above the fasting level was marked and fairly constant. The percentage of increase varied from 62 per cent to 133 per cent, with an average of 90 per cent. The general trend of the increase was around two levels, 70 per cent to 75 per cent and 100 per cent to 120 per cent. To be on the safe side, at this stage we have made our standard of normalcy in this test for liver function in children an increase of at least from 50 to 60 per cent above the fasting blood urea four hours after a protein meal of 1 Gm per kilogram. The work of Van Slyke<sup>9</sup> and his

TABLE 1—*Increase in Blood Urea After Protein Meal in Children with Apparently Normal Livers*

No	Name	Sex	Weight, kg	Diagnosis	Protein Eaten, Gm	Blood Urea Nitrogen per 100 Cc Blood	Increase of Blood Urea in 4 Hours, per Cent
1	R M	M	22	Malnutrition	22	Fasting, 11.2 mg 2 hours, 12.0 mg 4 hours, 19.6 mg	75
2	H G	M	38	Chorea	38	Fasting, 12.0 mg 2 hours, 14.0 mg 4 hours, 21.0 mg	75
3	M B	M	40	Herpes	40	Fasting, 12.6 mg 2 hours, 14.0 mg 4 hours, 21.0 mg	70
4	A W	M	21	Chorea	21	Fasting, 11.2 mg 4 hours, 18.2 mg	62
5	H H	M	32	Postencephalitis	32	Fasting, 11.2 mg 2 hours, 19.6 mg 4 hours, 23.8 mg	112
6	L R	M	23.5	Chorea	23.5	Fasting, 11.0 mg 2 hours, 12.4 mg 4 hours, 19.4 mg	76
7	E D	F	26	Hernia	26	Fasting, 12.6 mg 2 hours, 26.4 mg 4 hours, 29.4 mg	133
8	O C	F	31	Mild convalescent rheumatism	31	Fasting, 15.4 mg 2 hours, 21.0 mg 4 hours, 33.6 mg	121
9	R L	F	27.5	Mild rheumatism	27.5	Fasting, 14.0 mg 4 hours, 25.0 mg	79

co-workers and of Morgulis,<sup>10</sup> which showed an immediate deamination and urea formation by the liver after a protein meal, led us to conduct a short investigation to determine whether this was a specific effect of the protein or whether it was the stimulus of any food on this function of the liver. Accordingly, in three of our control cases we determined the blood urea at two and four hour intervals after a glucose meal. The results are given in table 2.

From the foregoing figures we see that the ingestion of glucose did not affect the blood urea, and we must conclude that the protein or amino-acid molecule alone in the intestinal tract has the faculty of stimulating the liver to deamination before the amino-acid of the blood is increased.

In table 3 are summarized the results of tests for liver function in cases in which there was definite hepatic disorder both during and after the liver was injured. The first was a case of pneumonia which was marked by jaundice and large liver. All tests for liver function yielded subnormal results, while the liver was enlarged and the patient icteric.

TABLE 2—*Increase in Blood Urea after Glucose Meal in Children with Apparently Normal Livers*

No	Name	Sex	Weight, Kg	Diagnosis	Glucose Ingested, Gm	Blood Urea Nitrogen per 100 Cc Blood	Increase of Blood Urea in 4 Hours, per Cent
1	L R	M	23.5	Chorea	53	Fasting, 12.4 mg 2 hours, 11.2 mg 4 hours, 12.6 mg	0
2	F D	F	26	Hernia	60	Fasting, 14.0 mg 2 hours, 14.0 mg 4 hours, 14.0 mg	0
3	O C	F	31	Rheumatism	70	Fasting, 11.0 mg 2 hours, 12.4 mg 4 hours, 11.0 mg	0

TABLE 3—*Tests for Liver Function in Children with a Definite Pathologic Condition of the Liver as Evidenced by Jaundice and Large Liver*

Name	Sex	Weight, Kg	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test	Van den Bergh Test	Urine Urobilin
R J	M	36	12/14/25	Fasting, 18.2 mg 4 hours, 18.2 mg Increase, 0		15 min 25% 1 hour 20% (P T P)	1 40,000	Present 1 800 dilution
			12/23/25	Fasting, 11.2 mg 4 hours, 16.8 mg Increase, 50%		1 hour, 0	1 200,000	Present 1 10 dilution
E S	M	30	3/ 1/26	Fasting, 12.6 mg 4 hours, 15.24 mg Increase, 22%	0 105 0 100 0 105 0 105	½ hour, 30% 1 hour, 30% (B S P)	1 34,000	Present 1 150 dilution
			3/14/26	Fasting, 14.0 mg 4 hours, 16.8 mg Increase, 20%	0 098 0 100 0 110 0 100	½ hour, 10% (B S P)	1 100,000	Present 1 70 dilution
			3/19/26	Fasting, 12.8 mg 4 hours, 19.4 mg Increase, 55%			1 300,000	Present 1 10 dilution
W F	M	28	8/27/26	Fasting, 14.0 mg 4 hours, 16.8 mg Increase, 20%			1 100,000	
			9/ 3/26	Fasting, 14.8 mg 4 hours, 23.8 mg Increase, 60%			1 400,000	

Especially to be noted is the fact that at this stage a protein meal did not cause an increase in the blood urea at the end of four hours. After the pneumonia had completely resolved, the jaundice had disappeared and the liver had become normal in size, tests for liver function were normal, including the protein test, which then caused a 50 per cent increase in four hours. The second case is one of so-called catarrhal

jaundice which is now generally regarded as a hepatitis<sup>24</sup> Tests for liver function during the stage of jaundice and enlarged liver revealed subnormal hepatic function, with the exception of the levulose tolerance test The protein test caused a 22 per cent increase in the fasting blood urea, which two weeks after remained the same, but which later rose to 55 per cent, or a normal increase, contemporaneously with a return of the blood bilirubin to normal The clinical data at this period of normalcy revealed a liver normal in size and free from icterus The third patient was suffering from the same disease, and substantially the same results were obtained with these tests

TABLE 4—*Children with Cardiac Disease and Enlarged, Tender Liver and Decompensation Showing Changing Tests for Liver Function During and after Decompensation*

Name	Sex	Weight, Kg	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test (Bromsulphalein)	Van den Bergh Test	Urine Urobilin
E L	M	18	3/ 8/26	Fasting, 12.6 mg 4 hours, 14.0 mg Increase, 11%	0.100 0.110 0.110 0.100	½ hour, 5%	1 200,000	Absent
			3/19/26	Fasting, 12.6 mg 4 hours, 19.6 mg Increase, 55%			1 400,000	
L B	F*	23	6/ 3/26	Fasting, 18.2 mg 4 hours, 22.4 mg Increase, 22%			1 150,000	
A W	M	18	6/14/26	Fasting, 16.8 mg 4 hours, 18.2 mg Increase, 8%	0.092 0.135 0.095 0.092	½ hour, neg	1 300,000	Trace
			6/29/26	Fasting, 12.6 mg 4 hours, 19.6 mg Increase, 5%				
A S	M	24	5/16/26	Fasting, 11.2 mg 4 hours, 15.4 mg Increase, 36%	0.100 0.115 0.110 0.100	½ hour, neg	1 300,000	Absent
			6/ 3/26	Fasting, 12.6 mg 4 hours, 18.2 mg Increase, 45%				
I S	M	28	3/19/26	Fasting, 16.8 mg 4 hours, 18.0 mg Increase, 7%		½ hour, neg	1 400,000	Trace
			3/26/26	Fasting, 15.4 mg 4 hours, 28.0 mg Increase, 85%				

\* Severe cardiac with tremendous liver The patient died within a short time

Another group, composed of children with heart disease, was also studied to determine whether the clinical symptoms of an enlarged liver denoting decompensation and the commonly encountered subicteric tint were associated with signs of a lowered function of the liver, as suggested by some workers<sup>25</sup> For this purpose cases with signs of decom-

<sup>24</sup> McNee (footnote 4, second reference) and Andrews (footnote 4, third reference)

<sup>25</sup> Andrews, C H (footnote 4) Ottenberg, R, Rosenfeld, S, and Goldsmith, L The Clinical Value of the Serum-Tetrachlorophenolphthalein Test for Liver Function, Arch Int Med 34 206 (Aug) 1924

pensation and an enlarged liver were investigated at the same time as cardiac cases without signs of decompensation but with a normal liver according to physical examination. The data are given in table 4.

Analysis of the data reveals that the levulose tolerance tests have been of little value in revealing liver hypofunction. The van den Bergh and the protein tests for urea formation have given positive results. The other liver tests in this group have not thrown much light on the function of the liver. The slight increase in blood bilirubin as shown by the van den Bergh reaction in patients with compensated heart disease is probably due to hemolysis with consequent increase of the blood bilirubin. This is evident by the increasing anemia in rheumatic fever and also suggested by the indirect reaction of the van den Bergh test, as was pointed out by Fishberg.<sup>26</sup> It must be stated here, however, that the latter test is far from an unfailing guide to hemolysis, as shown in

TABLE 5—*Tests for Liver Function in Cardiac Children not Decompensated, with Impalpable Livers*

Name	Sex	Weight, Kg	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test	Van den Bergh Test	Urine Urobilin
J. B.	M	22	Fasting, 11.2 mg 4 hours, 18.2 mg Increase, 62%	0.100 0.110 0.105 0.100	½ hour, neg	1:170,000	Absent
R. L.	F	23.5	Fasting, 14 mg 4 hours, 25 mg Increase, 78%	0.090 0.105 0.105 0.100	½ hour, neg	1:200,000	Absent
C. O.	F	31	Fasting, 15.4 mg 4 hours, 21.0 mg Increase, 38%		½ hour, neg	1:300,000	Absent

the cases of decompensated heart disease when other tests indicated that the increased bilirubin was due to diminished hepatic function. A high urea index for the blood in cases of cardiac decompensation when the patient is fasting is known to be due to renal deficiency.

The function of the liver is often disturbed in cases of severe pneumonia. As evidence, we can adduce the clinical facts of hepatic enlargement and jaundice, and the laboratory aid of tests of function in such cases,<sup>27</sup> particularly the retention of dye in toxic cases of pneumonia. With this point in mind, we studied some cases of toxic pneumonia in contrast to mild cases of pneumonia when there was little reason to suspect involvement of the liver, studying the function of the liver immediately after the crisis and again after complete convalescence, when indicated.

<sup>26</sup> Fishberg, A. M. Jaundice in Myocardial Insufficiency, *J. A. M. A.* **80** 1516 (May 26) 1923.

<sup>27</sup> Ottenberg, R., Rosenfeld, S. and Goldsmith, L. (footnote 25) Harris, B. R. Alterations in Liver Function as an Index of Toxemia in Pneumococcus Lobar Pneumonia, *J. Clin. Investigation* **20**: 6 (Aug. 20) 1926.

In cases of toxic pneumonia, the protein test for liver function in three of four cases revealed subnormal urea formation by the liver. In two of these, the van den Bergh test and the increased excretion of urobilin in the urine were further evidence of the impaired function of the liver. Before the children were discharged from the hospital, the protein tests, together with the other tests, had become normal demon-

TABLE 6—*Liver Function Tests in Cases of Toxic Pneumonia*

Name	Sex	Weight, Kg	Date	Changes in Blood Urea Nitrogen After Protein	Levu lose Test	Dye Test	Van den Bergh Test	Urine Uro bilin
I L	M	20	2/ 2/26	Fasting, 14.0 mg 4 hours, 16.8 mg Increase, 20%	0.075 0.190 0.100 0.094	½ hour, 0	1:400,000	Absent
			2/15/26	Fasting, 11.0 mg 4 hours, 18.0 mg Increase, 65%				
F S	F	19	2/26/26	Fasting, 19.6 mg 4 hours, 33.6 mg Increase, 71%	0.080 0.100 0.100 0.090	½ hour, 0	1:400,000	Trace
A S	F	23.5	3/27/26	Fasting, 14.3 mg 4 hours, 18.6 mg Increase, 31%	0.100 0.114 0.115 0.102	½ hour, 0	1:125,000	Absent
			4/10/26	Fasting, 12.4 mg 4 hours, 21.6 mg Increase, 77%			1:140,000	
R J	M	36	12/14/25	Fasting, 18.2 mg 4 hours, 18.2 mg Increase, 0		15 min., 25% 1 hour, 20% (P.T.P.)	1:40,000	1:800 dilution
			12/23/25	Fasting, 11.2 mg 4 hours, 16.8 mg Increase, 50%		1 hour, 0	1:200,000	1:10 dilution

TABLE 7—*Liver Function Tests in Cases of Mild Pneumonia*

Name	Sex	Weight, Kg	Date	Changes in Blood Urea Nitrogen After Protein	Levu lose Test	Dye Test (Bromsulphalein)	Van den Bergh Test	Urine Urobilin
C C	F	19	12/13/25	Fasting, 11.2 mg 4 hours, 16.8 mg Increase, 50%		0	1:400,000	1:10 dilution
E D	F	17	1/ 9/26	Fasting, 11.2 mg 4 hours, 18.0 mg Increase, 60%	0.110 0.120 0.107 0.105	0	1:200,000	1:10 dilution
H N	F	20	2/14/26	Fasting, 18.0 mg 4 hours, 26.6 mg Increase, 48%	0.120 0.135 0.105 0.096	½ hour, 5%	1:400,000	Absent

strating the rapid recovery of the liver in convalescence after pneumonia. The dye test was positive in only one case, and the levulose metabolism was normal in every case. Mild cases of pneumonia revealed little change in the function of the liver. In passing, we may note that the initially high fasting urea sometimes encountered in infections had been noted and commented on previously.<sup>23</sup>

Another group studied was a miscellaneous one in which, however, there was reason to suspect disturbance of the function of the liver. The results are given in table 8.

These results show that a patient who had leukemia and a large liver did not reveal a demonstrable lowering of the function of the liver according to our tests for liver function. A patient with Hodgkin's disease showed a definite diminution of the function of the liver, as shown by increased blood bilirubin, excessive urobilin in the urine and the protein test which resulted in only 27 per cent increase of the blood urea in four hours. A patient suspected of having abdominal tuberculosis with an easily palpable liver showed only a 28 per cent increase of blood urea four hours after a protein meal, which would make us feel that the

TABLE 8—Liver Function Tests in a Group of Miscellaneous Cases

Name, Sex, Weight	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test, Bromsul- phalein	Van den Bergh Test	Dye Test	Urine Urobilin	Diagnosis and Comment
E. M. F. 20 Kg	12/24/25	Fasting, 14.0 mg 4 hours, 22.4 mg Increase, 60%		1,400,000	15 min 5% 1 hour, 0	1:20 dilution	Leukopenic leukemia with large liver
P. D. M. 34 Kg	5/16/26	Fasting, 11.0 mg 4 hours, 14.0 mg Increase, 27%		1,800,000	½ hour, 0	68 mg	Hodgkin's disease with large liver
A. M. M. 19 Kg	4/30/26	Fasting, 15.4 mg 4 hours, 19.6 mg Increase, 28%	0.100 0.110 0.110 0.100 0.100	1,200,000	½ hour, 0	Absent	Abdominal tubercu- losis (?) with large liver
A. D. M. 22.5 Kg	3/23/26	Fasting, 11.2 mg 4 hours, 11.2 mg Increase, 0	0.152 0.140 0.140 0.122	1,175,000	½ hour, 0		Ketosis due to food poisoning, blood sugar 0.31 on ad- mission and car- bon dioxide, 30, after treatment with insulin and glucose, clinical re- covery and normal function of liver attained
	3/30/26	Fasting, 11.2 mg 4 hours, 19.6 mg Increase, 75%	0.100 0.112 0.113 0.100	1,400,000	½ hour, 0		

enlarged liver meant liver injury. A patient with a severe case of ketosis showed a high fasting blood sugar with a practically normal levulose test, a slight increase of blood bilirubin and no increase in the blood urea four hours after the protein meal. After intensive insulin glucose therapy with forcing of fluids, the blood sugar returned to normal, the blood bilirubin reached its normal level and the protein meal caused a 75 per cent increase of the blood urea in four hours—all indicative of recovery from the previously diminished liver function.

In these cases of liver injury, we have noticed that the most constant and most positive indicator of hepatic hypofunction was the protein test. This was frequently corroborated by other tests for liver function that were simultaneously positive, and also by the fact that when the liver returned to normalcy, the protein test caused a normal increase in the

blood urea In no case was a test for liver function undoubtedly positive when the protein test was normal It may be worth noting that after the protein test, the best guide to liver injury was the van der Bergh test, then the dye test and the estimation of the urobilin in the urine, and last, the levulose test, which we found to be a poor test for liver function

#### CONCLUSION

1 A new test for liver function is described, based on the normal conversion by the liver of amino-acids to urea

2 After a protein meal of 1 Gm per kilogram of weight, the blood urea will increase as the blood sugar does after a glucose meal Normally the blood urea will increase at least from 50 to 70 per cent above the fasting level in four hours

3 In cases of liver injury, this increase of the blood urea after a protein meal is much diminished, usually below 50 per cent, and sometimes an increase does not result in four hours

4 Other tests for liver function have corroborated this test of sub-normal hepatic function

5 When the liver again becomes normal, the protein test also causes a normal increase in blood urea

# THE DIAMETER OF RED BLOOD CELLS IN HEALTH AND IN ANEMIA

A NEW METHOD OF MEASUREMENT \*

A R McCORMICK, M D

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It is an established fact that the average diameter of red blood cells in secondary anemia is decreased, and that many macrocytes are found in pernicious anemia. Occasionally there is difficulty in estimating the size of the cells by merely looking at the blood smear, especially if there is much distortion, or if the size and shape vary only slightly from normal. The exact measurement of the cells and the plotting of curves showing their distribution according to size may thus aid in the differentiation of anemias. My purpose was to find a practical and accurate method of measuring the diameter of the red blood cells.

Price-Jones<sup>1</sup> and others made stained films of blood, projected the image on to a sheet of paper, then measured the minimum and maximum diameters, and used the average as the diameter of the cell. In each film 500 cells were measured.

Grosh and Stifel<sup>2</sup> also used stained films, but measured the cells by means of a Leitz ocular micrometer. This is a glass disk which has a scale engraved on it, and which fits into the ocular of the microscope. The image of the scale focuses on the image of the blood film. The slide is moved by a mechanical stage, and only the round cells that happen to lie on the scale are measured.

## TECHNIC

My method was to dilute the fresh blood with Hayem's solution, as in making a count of the red blood cells. The cells were thus measured in a moist preparation. Price-Jones<sup>1</sup> has shown that the diameter of the red blood cells in a dried film are smaller than the diameter of those in a moist preparation. I used a Bausch and Lomb Filar ocular micrometer to measure the diameters. As one looks into the ocular of the instrument, a vertical hair line is seen. This is a small wire that moves on a slide by means of a micrometer screw. Attached to the screw is a drum-head on which is a scale divided into fifty parts. The micrometer fits into the draw tube of the microscope and is secured by a set screw.

It is important that the apparatus be accurately calibrated, since there is too much error in depending on the theoretical magnification of the lenses. The instrument for this experiment was calibrated with an accurate stage micrometer.

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\* From the Medical Clinic, Mercy Hospital

1 Price-Jones, Cecil. The Diurnal Variations in the Size of Red Blood Cells, *J Path & Bact* **23** 71 (Dec) 1920

2 Grosh, L C, and Stifel, J L. The Diameter of the Red Blood Cells in the Differentiation of Anemias, *Arch Int Med* **36** 874 (Dec) 1925

obtained from the Bureau of Mines of this city and a Bausch and Lomb counting chamber. With the tube length of 160 mm and using the high power lens, it was found that five divisions on the scale of the drum-head was equal to 1 micron. With the slide used in measuring the cells on the stage of the microscope, it was found that the tube length had to be changed to 170 mm to give this reading. This final setting was checked by a Filar ocular micrometer from the Bureau of Mines. In all measurements the same apparatus was used. By means of the micrometer and a mechanical stage each cell can be individually measured accurately. Only round cells were measured, but no selection of these was made. In this way the one measurement served as the diameter of the red blood cell.

The normal curve was obtained by measuring the diameters of 2,000 red blood cells of ten normal persons. The average diameter was calculated, and the scale

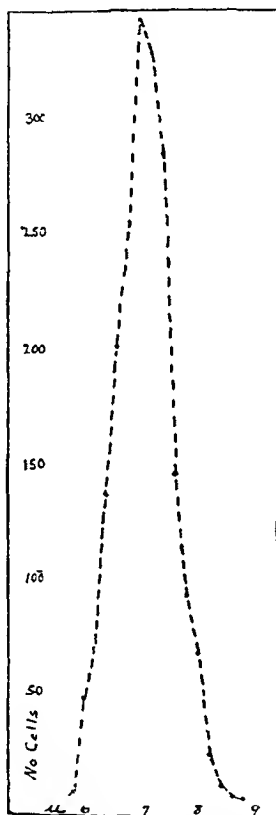


Chart 1—Author's normal curve (2,000 cells), the average diameter was 7.32 microns

was reduced to that of 200 and 100 cells. Usually 200 cells were measured, but it was found that a satisfactory curve for diagnosis could be obtained by estimating the size of 100 cells. The normal average diameter in this series was 7.32 microns. The average normal diameter as determined by Price-Jones was 7.21 microns, by Hampson and Shackle, 7.23 microns<sup>3</sup> and by Grosh and Stifel, 7.42 microns<sup>2</sup>.

#### NORMAL CURVE

The normal curve is symmetrical (chart 1). There is only one peak, which is well defined and which occurs at about the average diameter. The sides of the curve are almost straight lines. The difference between

<sup>3</sup> Hampson, A. C., and Shackle, J. W. Megalocytic and Nonmegalocytic Anemia, *Guy's Hosp. Rep.* 74:193 (April) 1924.

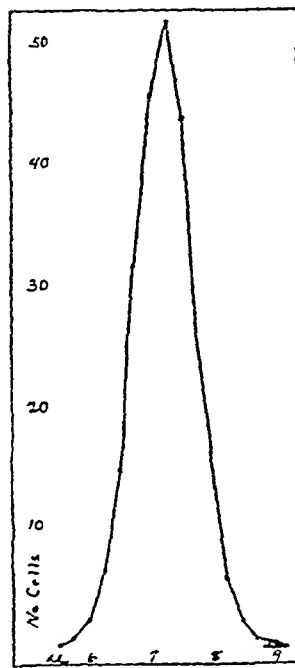


Chart 2—Price-Jones normal curve (10,000 cells reduced to scale of 200 cells); the average diameter was 7.21 microns

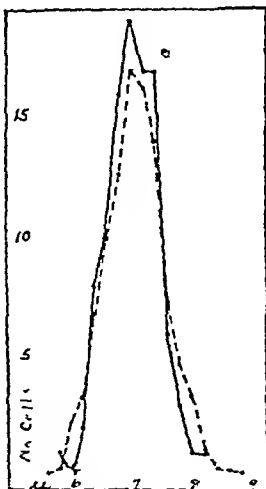


Chart 3

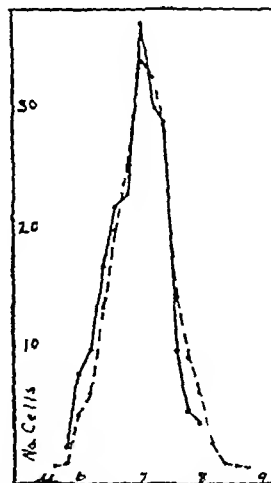


Chart 4

Chart 3—Normal curve (100 cells), the average diameter was 7.103 microns. The broken line represents the author's normal curve, the average diameter was 7.32 microns

Chart 4—Normal curve (200 cells) the average diameter was 6.94 microns. The broken line represents the author's normal curve, the average diameter was 7.32 microns

the smallest and the largest cell was only 3.2 microns, showing the slight normal anisocytosis. The normal curve as obtained by Price-Jones<sup>1</sup> (chart 2) closely resembles our normal curve. The individual normal curves approach the normal curve closely (charts 3 and 4), although the averages differ. The difference between the smallest (6.9 microns) and the largest (7.6 microns) individual normal average diameters was 0.7 micron.

#### SECONDARY ANEMIA

The curve of secondary anemia is somewhat asymmetrical, but not to a marked degree (charts 5, 6 and 7). It is found to the left of the normal curve. The average diameter is smaller than normal. There is

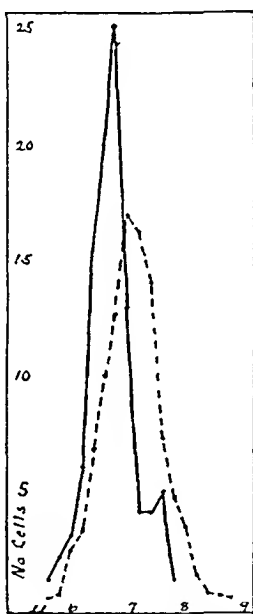


Chart 5—Secondary anemia (cancer of stomach) the average diameter of 100 cells was 6.72 microns. The broken line represents the author's normal curve, the average diameter was 7.32 microns.

usually only one peak, and it is almost as well defined as normal. In the present series the variation in the size of the cells was usually less than normal, but it may be greater.

#### PERNICIOUS ANEMIA

The curve of pernicious anemia is asymmetrical. The greater part of the usual curve lies to the right of the normal curve (chart 8). The average diameter is greater than normal. The curve is flattened out, there being many peaks. The anisocytosis is marked, and the degree varies in general directly with the anemia, but there is no relation between the average diameter and the degree of variation.

In a few of the cases of pernicious anemia which I measured, a different type of curve was obtained. These cases were of an acute type with red cell counts below one million, although not all the cases with so severe an anemia showed this type of curve. The curve is low and spread out, even more so than is usual in pernicious anemia, but it lies to the left of the normal curve. The average diameter is below normal. There were no large irregular cells in this type, all the cells being small and round or oval. In one case (chart 9) not one macrocyte was seen. Clinically these were typical cases of pernicious anemia. The toxin was so severe that it produced degenerative changes in the bone marrow so that only cells that were small and poor in hemoglobin were formed. Thus according to these observations, the

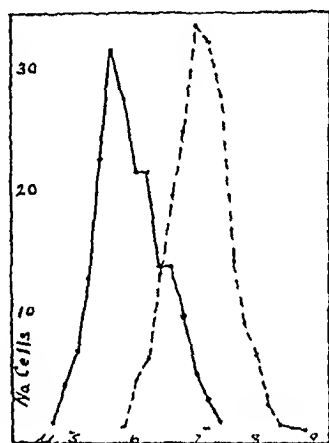


Chart 6

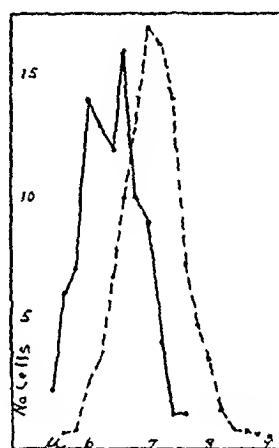


Chart 7

Chart 6—Secondary anemia, the average diameter of 200 cells was 5.90 microns. The broken line represents the author's normal curve, the average diameter was 7.32 microns.

Chart 7—Secondary anemia (chlorosis), the average diameter of 100 cells was 6.39 microns. The broken line represents the author's normal curve.

Differentiation of the anemias cannot be based entirely on the average diameter but on the type of curve found, that is, on the distribution of the cells according to size.

The typical curve of pernicious anemia, as first described, was also found in one case during a remission (chart 10). The patient was receiving the usual treatment. There is usually less anisocytosis at this time than during the active stage of the disease.

The megalocytic type of curve has been reported as occurring in sprue,<sup>4</sup> infantilism<sup>3</sup> and *Bothriocephalus latus* infestation.<sup>4</sup>

<sup>4</sup> Hampson, A. C., and Shackle, J. W. (footnote 3) Passey, R. D. Measurements of the Red Blood Cells in the Anemias of Sprue and *Bothriocephalus Latus* Infection, Guy's Hosp. Rep. **74** 329 (July) 1924.

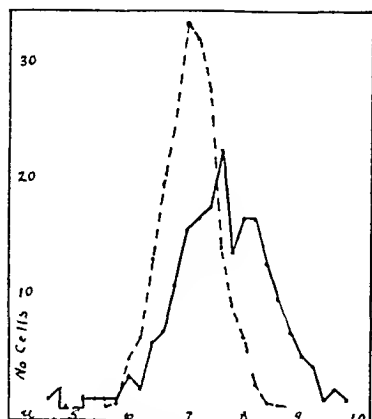


Chart 8

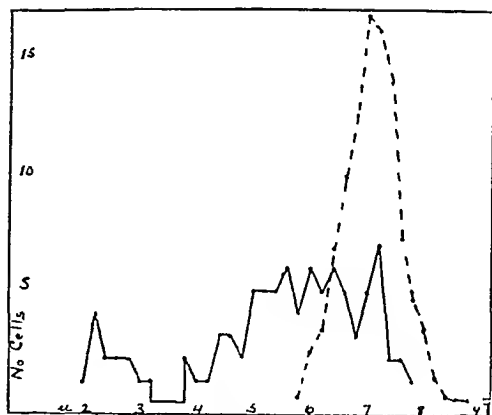


Chart 9

Chart 8—Pernicious anemia (1,200,000 red blood cells), the average diameter of 200 cells was 8.12 microns. The broken line represents the author's normal curve.

Chart 9—Pernicious anemia (500,000 red blood cells), the average diameter of 100 cells was 5.45 microns. The broken line represents the author's normal curve.

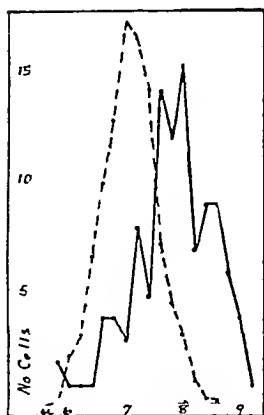


Chart 10

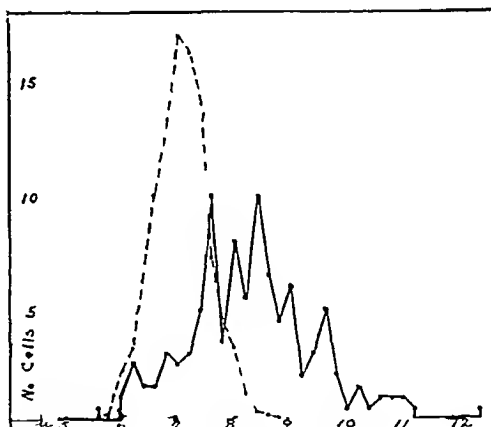


Chart 11

Chart 10—Pernicious anemia remission (80 per cent, 4,100,000), the average diameter of 100 cells was 7.76 microns. The broken line represents the author's normal curve.

Chart 11—Pernicious anemia (2,810,000 red blood cells) before treatment, July, 1926. The average diameter of 200 cells was 8.34 microns. The broken line represents the author's normal curve.

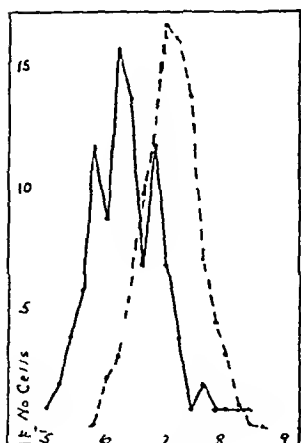


Chart 12

Chart 12—Pernicious anemia (3,720,000 red blood cells) after treatment, October, 1926. Average diameter of 100 cells was 5.84 microns. The broken line represents the author's normal curve.

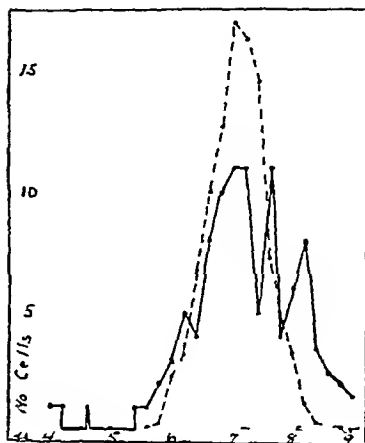


Chart 13

Chart 13—Pernicious anemia (1,000,000 red blood cells) before treatment, Sept 27, 1926. The average diameter of 100 cells was 7.94 microns. The broken line represents the author's normal curve.

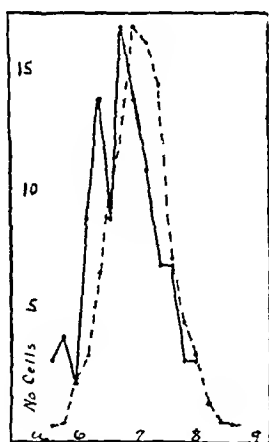


Chart 14

Chart 14—Pernicious anemia (2,650,000 red blood cells) after treatment, Oct 14, 1926. The average diameter was 6.94 microns. The broken line represents the author's normal curve.

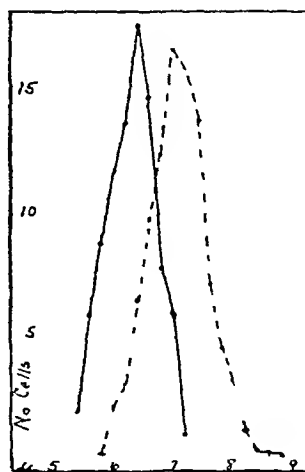


Chart 15

Chart 15—Pernicious anemia (2,700,000 red blood cells) after treatment, Nov 12, 1926. The average diameter of 90 cells was 6.3 microns. The broken line represents the author's normal curve.

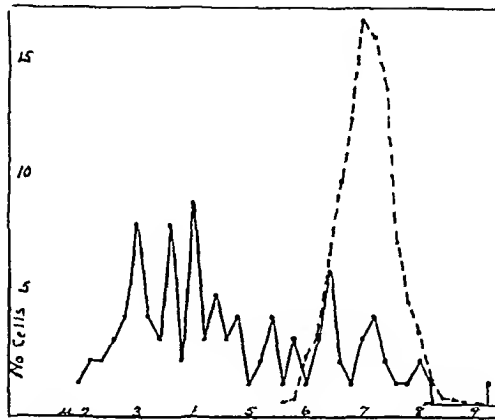


Chart 16—Pernicious anemia (900,000 red blood cells) before treatment, April, 1926 The average diameter of 100 cells was 474 microns The broken line represents the author's normal curve

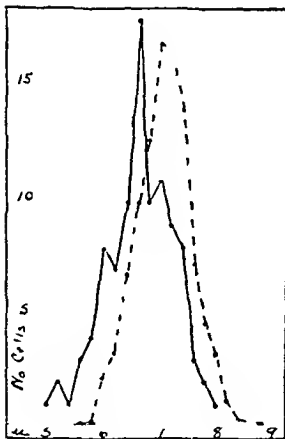


Chart 17

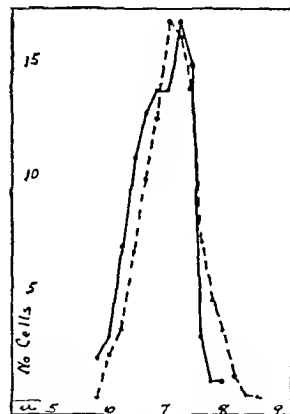


Chart 18

Chart 17—Pernicious anemia (2,800,000 red blood cells) after treatment, May, 1926 The average diameter of 100 cells was 665 microns The broken line represents the author's normal curve

Chart 18—Pernicious anemia (4,100,000 red blood cells) after treatment, Aug 12, 1926 The average diameter of 100 cells was 688 microns The broken line represents the author's normal curve

An interesting change occurred in the curves of pernicious anemia in those cases in which the patients had been treated by the liver diet according to Minot and Murphy.<sup>5</sup> Both types of curves assumed a form resembling that found normally or in secondary anemia. The average diameter that was larger than normal became smaller than normal. Early in the treatment the curve was still asymmetrical (charts 11 and 12) but moved to the left of the normal curve, whereas formerly it was in great part on the right, this is due to the disappearance of the macrocytes. Later in the course of the treatment, the curve became symmetrical (charts 13, 14 and 15). In the type of pernicious anemia in which the average diameter was smaller than normal, it became larger but still less than normal (charts 16, 17 and 18). In the case illustrated by chart 18 the curve closely approaches normal. The curves showing the change under the treatment outlined by Minot and Murphy are to be contrasted with those in the case previously shown in remission (chart 10) in which the usual method of treatment was used. Not all cases respond to the liver diet. In one case, a typical curve of pernicious anemia persisted up to the time of death, in spite of the treatment.

#### CONCLUSIONS

1. A practical and accurate technic has been described for measuring the diameter of the round red blood cells.
2. The measurement of the cells and plotting of the curves are frequently of great diagnostic value.
3. The curves in normal cases and those in cases of secondary anemia are characteristic and constant.
4. In pernicious anemia two types of curves were found.
5. The average diameter is not always increased in pernicious anemia.
6. Treatment of patients with pernicious anemia by the method described by Minot and Murphy produces definite changes in the size of the red blood cells.

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<sup>5</sup> Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**: 470 (Aug. 14) 1926.

# CEREBROSPINAL FLUID IN NEPHRITIS \*

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It seems fair to say that the increasing difficulty in the diagnosis of cases with cerebral, or rather central nervous system, manifestations has not been lessened by the increased data concerning epidemic encephalitis and its bizarre symptomatology. One cannot help but feel that the recognition of this feature of encephalitis has led in great measure to a certain laxness in following puzzling cases to a definite conclusion.

Discussion as to the ultimate diagnosis in one fatal case gave rise to the question whether an apparently noninflammatory condition of the central nervous system could produce a spinal fluid like that in epidemic encephalitis or in other inflammatory conditions. Is increased protein (albumin and globulin) in the cerebrospinal fluid always a sign of inflammation? Could chronic nephritis with uremia, a supposedly non-inflammatory condition in relation to the central nervous system, account for a similar picture?

Baar<sup>1</sup> studied the diagnostic value of increased globulin in spinal fluids, particularly in diseases of children, and noted the presence of an increase in uremia. He noted that the increase in protein was so marked as to suggest tuberculous meningitis. Alpers<sup>2</sup> reviewed the literature, compiling ninety-eight cases. We shall refer to this review in the course of this article. No attempt to establish a definite picture for the cerebrospinal fluid in chronic nephritis has previously been made and little work has been performed particularly in reference to the protein content.

We have had the opportunity to study the cerebrospinal fluid in twenty-two cases of nephritis.

## METHODS

The determinations of sugar in blood and in cerebrospinal fluid were made by Folin's method,<sup>3</sup> but in preparing the protein-free filtrate from spinal fluid

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\* From the Department of Diseases of Children, Columbia University, College of Physicians and Surgeons, and the Children's Medical Division and the Department of Pathology, Bellevue Hospital.

1 Baar, H. The Diagnostic Value of Increased Globulin of the Spinal Fluid in Affections of Children, *Wien klin Wchnschr* **34** 614, 1921.

2 Alpers, B. J. Human Cerebrospinal Fluid in General System and Metabolic Diseases, *J Nerv & Ment Dis* **62** 265 (Sept) 1925.

3 Folin, O. *J Biol Chem* **38** 98, 1919.

one-fourth the usual quantities of 10 per cent sodium tungstate and two-thirds normal sulphuric acid were used, and the final dilution was 1:5 instead of 1:10, as in blood. For nonprotein nitrogen in blood the usual 1:10 filtrate and in spinal fluid the 1:5 filtrate were employed. The method of Folin and Wu<sup>4</sup> was followed. The method adopted for uric acid was that of Folin<sup>5</sup> with the improved reagent.<sup>6</sup> The procedure of Folin and Wu<sup>7</sup> was followed for pre-formed creatinine.

Total nitrogen in spinal fluid was determined by a modification of the procedure of San Yin Wong,<sup>8</sup> hydrogen peroxide as suggested by Rose<sup>9</sup> being used instead of potassium persulphate. Occasionally the work was checked with the macro-Kjeldahl method.

The difference between the nonprotein nitrogen content and the total nitrogen when multiplied by 6.25 was taken as the protein content. This calculation seems to be more accurate when the nonprotein nitrogen is not excessively high. An example will make this clear. In one case the total nitrogen was 18 mg and the nonprotein nitrogen 10 mg, the protein content was 50 mg. In another case the total nitrogen was 216 mg and the nonprotein nitrogen 200 mg, the protein content was taken to be 100 mg. It is obvious that the error is much greater in the second case when one realizes that a hardly perceptible turn of the colorimeter screw will not make any difference in the first case, but an immense difference in the second. When it is necessary to dilute the cerebrospinal fluid for the estimation of nitrogen it is apparent that the error is in proportion to the dilution factor, and as the proportion of the various proteins is not constant in different fluids, it is apparent that an unknown error exists in the usual protein nitrogen factor, 6.25. An error of one division on the colorimeter vernier gives an error for the first case mentioned of approximately 2 per cent of protein. The same error for the second case, the cerebrospinal fluid being diluted 1:10 amounts to 6 per cent. This is without reckoning errors of dilution and other factors in the estimations of the nonprotein nitrogen. Supposing, however, that the nonprotein nitrogen in the second case were 16 mg, the protein would be 1250, and an error of one division on the vernier would reduce the protein figure to 1,244, a negligible error of 6 mg in 1,250, or less than 0.5 per cent.

Van Slyke's method<sup>10</sup> was used for chlorides in blood plasma and in cerebrospinal fluid. To determine the presence of albumin qualitatively the nitric acid ring test was used, and for globulin the Pandy reaction.

#### CEREBROSPINAL FLUID IN NEPHRITIS

The fluid in all cases was clear and, with one exception, colorless. In the exception, there was a faint yellow-green tinge. For obvious reasons, blood contaminated fluids are not included in this study.

Manometer readings were not taken, but in the majority of cases the pressure was increased as judged by the initial spurt from the needle and the rapidity of flow.

The cell count varied from 2 to 16 cells per cubic millimeter, all lymphocytes except in one case in which, with a count of 14, 50 per cent

4 Folin and Wu. *J Biol Chem* **38** 81, 1919.

5 Folin, O. *J Biol Chem* **54** 153 (Oct.) 1922.

6 Folin, O., and Trimble, H. *J Biol Chem* **60** 473 (June) 1924.

7 Folin and Wu. *J Biol Chem* **38** 81, 1919.

8 San Yin Wong. *J Biol Chem* **55** 431 (March) 1923.

9 Rose, A. R. *J Biol Chem* **64** 253 (June) 1925.

10 Van Slyke. *J Biol Chem* **58** 523 (Dec.) 1923.

were polymorphonuclears. In six, or 21 per cent, the count was higher than 10. (The presence of uremic symptoms has no relation to the cell count, nor, apparently, has the type of nephritis which is encountered.)

#### CHEMISTRY

*Sugar*—All fluids gave a reduction with Benedict's solution. The amount of sugar varied from 31 to 125 mg per one hundred cubic centimeters. If we take 70 mg as the upper normal value for cerebrospinal fluid sugar, then twelve, or 50 per cent, of the cases were higher than normal, only one fluid gave a low value, 31 mg.

In cases of chronic nephritis only, the average cerebrospinal fluid sugar was 82.8 mg for cases with uremic symptoms and 57.2 mg for those without uremic manifestation.

Normally, the ratio,  $\frac{\text{Cerebrospinal fluid sugar}}{\text{Blood sugar}}$ , varies from 40 to 65 per cent. In eleven of our cases, or 50 per cent, the ratio is high, averaging 74.3 per cent. In one case identical values were obtained for blood and cerebrospinal fluid, and in one case as low a ratio as 26 per cent was found. Except in tuberculous meningitis, we have never seen such a low ratio in a clear fluid.

The chlorides range from 562 to 807 mg per one hundred cubic centimeters, excluding postmortem fluids. The upper normal value is 750 mg. In nine, or 37.5 per cent of our cases, the chlorides were high, averaging 779 mg. The blood plasma chlorides in these cases were, with two exceptions, above the high normal of 590 mg per one hundred cubic centimeters.

Postmortem fluids excluded, the average amount of chlorides in cases of chronic nephritis is 727.5 mg for those with uremic manifestations and 784 for those without. The amount of chlorides was low in two cases, 562 and 620 mg. In these the blood plasma chlorides were also low, being, respectively 362 and 421 mg per one hundred cubic centimeters. In three cases low blood plasma chlorides, 538, 491 and 527 mg, were present with normal cerebrospinal fluid chlorides.

In fluids taken post mortem, the chlorides are exceptionally high—in one case 825 mg in a fluid drawn five minutes post mortem and 960 mg in a fluid drawn one hour after death.

*Comment*—Cerebrospinal fluid chlorides in chronic nephritis are generally not increased. Our figures show a value somewhat higher than normal for cases without uremic symptoms, namely, 784 mg.

It is noteworthy that the cerebrospinal fluid chlorides in our cases of chronic nephritis with edema are especially the same as in those without edema, being 746 mg per one hundred cubic centimeters in the former and 743 mg in the cases without edema. Mestrezat,<sup>11</sup>

11 Mestrezat, W. *Le liquide cephalo-rachidien*, Paris, A. Maloine, 1912.

Levinson,<sup>12</sup> and Boyd,<sup>13</sup> however, report higher figures for cerebrospinal fluid chlorides in chronic nephritis with edema. Their values range from 0.8 to 0.85 per cent (800-850 mg.)

*Nonprotein Nitrogen*—The nonprotein nitrogen ranged from 8 to 210 mg. per one hundred cubic centimeters and excluding the cases of acute nephritis, from 15 to 210 mg. In cases with uremic symptoms in which there was retention of nitrogen in the blood, the cerebrospinal fluid nonprotein nitrogen averaged 121 mg., in nonuremic cases with retention of nitrogen, 90.6 mg.

The ratio  $\frac{\text{Cerebrospinal fluid nonprotein nitrogen}}{\text{Blood nonprotein nitrogen}}$ , when there is not a retention of nitrogen, is 46 per cent. In this series the ratio in the presence of retention of nitrogen is 80 per cent.

*Protein*—Qualitative studies alone show a definite increase in albumin and globulin in the cerebrospinal fluid in cases of chronic nephritis. Acute nephritis, unless accompanied by uremic symptoms, does not show an increase. The quantitative observations agree closely with the qualitative determinations.

The normal cerebrospinal fluid protein content ranges from 20 to 50 mg. per one hundred cubic centimeters. The average protein content of all cases of chronic nephritis is 127 mg., of those cases with uremic symptoms the average is 133 mg., nonuremic cases show 111 mg. protein per one hundred cubic centimeters. There is, then, a marked increase in the protein content of cerebrospinal fluid in chronic nephritis, higher figures being obtained when uremic symptoms are present. With two exceptions all patients having over 100 mg. protein in the cerebrospinal fluid died. These two patients, one with 138 mg. and the other with 119 mg., left the hospital definitely unimproved and gravely ill. The outcome is unknown.

We must reiterate here what was pointed out in the discussion of the methods employed in this study. Though there is a definite and undoubted increase in the protein in the cerebrospinal fluid in cases of chronic nephritis, the quantitative protein figures must at this time be accepted more for their relative than for their absolute values owing to the nature of the methods perfected to date.

*Comment*—Alpers,<sup>2</sup> after studying the literature, concludes that "in uremia the spinal fluid changes are different from those in nephritis." On the basis of our study, what exists is not so much a difference in the observations grossly, but rather one of degree, depending on the severity of the condition. An attempt has not been made in this study to follow the "pure" and "secondary" or "associated" uremia classification of

12 Levinson, A. Cerebrospinal Fluid in Health and Disease, St. Louis, C. V. Mosby Company, 1923.

13 Boyd, W. Physiology and Pathology of the Cerebrospinal Fluid, New York, MacMillan, 1920.

Mollard and Froment<sup>14</sup> We have used the term uremia in its broad sense to denote those cases of chronic nephritis in which coma, lethargy, convulsions, twitchings or persistent vomiting have been prominent features

On this basis our data are not directly comparable to Alpers' study It is noteworthy, however, that although in his cases of "associated" or "secondary" uremia (namely uremia with demonstrable etiology according to Mollard and Froment) "the albumin content is qualitatively normal," all our patients with uremic symptoms showed an increase in the albumin as well as in the globulin content

It is interesting to speculate on the origin of the increased albumin and globulin in the cerebrospinal fluid in cases of nephritis The choroid plexus has been thought to act as a barrier between the blood and the subarachnoid fluid This plexus, with its permeability intact, is able, it is thought, to maintain a cerebrospinal fluid of fairly uniform composition It is the injury to this barrier, as a result of retained or elaborated toxins due to the nephritic disturbance, that is thought to account for the changes in the cerebrospinal fluid in chronic nephritis Monakow<sup>15</sup> extirpated the kidneys in rabbits and found what he described as a more or less typical vacuolization of the epithelial cells of the choroid plexus Our mercuric case with the history of having swallowed mercuric chloride did not show any of these changes in the choroid plexus at autopsy

Our figures show also that there is not a relationship between the amount of protein in the cerebrospinal fluid and the blood pressure, either systolic or diastolic The presence of an increased amount of sugar in the cerebrospinal fluid in chronic nephritis (50 per cent of this series) as well as in encephalitis adds to the difficulty of diagnosis

Whatever the theoretical considerations, from a clinical standpoint it is important to remember that the presence of increased protein in the cerebrospinal fluid can no longer be considered as the result of a purely inflammatory process in relation to the central nervous system It is not unreasonable to suppose that some obscure cases with symptoms of the central nervous system caused by uremia have possibly been termed cases of atypical encephalitis because of the increase in protein

#### CEREBROSPINAL FLUID IN ACUTE INFECTIOUS NEPHRITIS

*Acute Nephritis*—As only three cases are included in this study, the observations must be accepted with the reservations necessarily attendant on any conclusions drawn from so small a number Nevertheless, the observations are of interest and are presented here for the value attached to them as part of the study of cerebrospinal fluid in nephritis

14 Mollard and Froment Urea dans le liquide cephalo-rachidien et uremie nerveuse J de physiol et de path gen 2 263 1909

15 Monakow, P Uremia and Choroid Plexus, Schweiz Arch f Neurol u Psychiat 13 11, 1923

# Results of Tests on Blood and Spinal Fluid in Nephritis

Results of Tests on Blood and Spinal Fluid																				
No.	Sex	Age	Blood										Spinal Fluid				Urine			
			Nonprotein Nitrogen		Sugar		Chlorides		Blood		Qualitative		Albumin	Colloid Gold	Protein	Casts	Max.imum Pressure	Eye Changes	Convul-sions	Edema
			Blood	Spinal Fluid	Blood	Spinal Fluid	Blood	Spinal Fluid	Blood	Spinal Fluid	Cells	Albumin								
1	M	33	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2	M	47	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
3	M	26	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
4	M	10	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
5	M	26	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
6	M	21	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
7	M	33	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
8	M	30	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
9	M	30	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
10	M	35	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
11	M	12	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
12	M	40	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
13	M	30	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
14	M	39	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
15	M	65	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
16	F	38	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
17	F	41	Chronic Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
18	F	3 mo	Acute Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
19	M	38	Acute Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
20	M	3	Acute Nephritis	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
21	F	31	Nephritic Toxicity	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
22	M	26	Mercuric Chloride Poisoning	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

In this table a/c means anticomplementary, P, polymorphonuclears, L, lymphocytes, G, granular and hyaline, H, hyaline, qns, not sufficient quantity

The fluid in every case was clear and under normal pressure. The cell counts were 7, 4 and 15 cells, respectively, all lymphocytes.

The cerebrospinal fluid nonprotein nitrogen was normal and bore the normal relationship to the blood nonprotein nitrogen, averaging 48 per cent. Attention must be called to the fact that in none of our cases of acute nephritis was there any retention of nitrogen.

The cerebrospinal fluid sugar averaged 66 mg, or 65 per cent of the blood sugar.

The chloride content was normal, our figures being 690, 749, and 725 mg per one hundred cubic centimeters, averaging for all three cases 126 per cent of the blood plasma chlorides.

Only the case with the uremic symptoms showed an increase in protein, having 75 mg per one hundred cubic centimeters. The other two were normal, being 25 and 36 mg, respectively.

*Comment*—Judged on the basis of the few cases studied, the cerebrospinal fluid in uncomplicated acute nephritis is normal. The protein content both qualitatively and quantitatively is normal except when uremic manifestations are present. In case 19, the patient was markedly stuporous at the time of the lumbar puncture, and the fluid showed an increase in protein. Leopold and Bernard<sup>16</sup> report two cases of acute nephritis in children, one with uremic symptoms. The cerebrospinal fluid of this case did not show an increase in globulin, but the cell count was high, 60.

We wish to discuss two of our cases separately, as they cannot, with any definiteness, be placed in any of the more usual classifications.

#### REPORT OF CASES

*Toxaemia of Pregnancy with Nephritis*—E. R., a colored woman, aged 31, a tertiodecipara, who was admitted to the obstetrical service April 7, 1926, as non-urgent, complained chiefly of headache, and the appearance of spots before the eyes during the past few weeks.

The patient had had trouble with most of the previous pregnancies, requiring surgical intervention before full term. One year ago, when thirty weeks pregnant, she had had a condition similar to that for which she now was admitted.

The physical examination showed a stout colored woman, somewhat dyspneic, not acutely ill, and not in labor. The heart was enlarged to the left, the lungs were normal, pregnancy was of about six months' duration, the blood pressure was systolic 270, and diastolic 150, both disks were blurred.

She suddenly developed convulsions, went into coma and failed to rally despite stimulation. The blood pressure dropped from 270 systolic and 150 diastolic to 76 systolic and 44 diastolic some hours before death, which occurred about thirty hours after admission.

The cerebrospinal fluid was clear, under increased pressure, and contained a normal number of cells. Protein in the first puncture was definitely increased, being 175 mg per one hundred cubic centimeters and falling to 81 in the post-mortem cistern fluid. In addition to the increased protein, the outstanding feature

16 Leopold and Bernard. Chemistry of Spinal Fluid, Am J Dis Child **13** 34 (Jan) 1917.

was the exceedingly low cerebrospinal fluid sugar, 31 mg, which was only 26 per cent of the blood sugar. To our knowledge, this low percentage in a clear fluid has been reported previously only in tuberculous meningitis. The colloidal gold curve, 2,221,110,000, of itself is suggestive of a pathologic change in the central nervous system, but the blood and cerebrospinal fluid negative Wassermann reactions tend to rule out, though not definitely, of course, any specific infection as the underlying factor.

*Mercuric Chloride Poisoning*—A. D., aged 36, entered the hospital March 11, 1926, with the history of having swallowed mercuric chloride (one-half teaspoonful of powder in water). He soon became nauseated and vomited. His stomach was lavaged shortly afterward. He had not had any cardiorespiratory condition or nocturia (measles and diphtheria in infancy). The patient was sitting up comfortably in bed, the pupils were equal and reacted to light, the edges of the gums were bluish and slightly reddened, there was no edema, the knee reflex was present.

The patient had almost complete anuria from the very onset and failed to rally despite the administration of sodium thiosulphate in gram doses daily, intravenously, and daily colonic irrigations. He died six days after admission.

On March 16 a spinal puncture showed a marked increase in nonprotein nitrogen and sugar, but the amount of chlorides was normal. The protein content was 119 mg, a definite increase. The cell count was normal.

*Autopsy*—Autopsy showed the typical gross kidney observations of mercuric chloride poisoning—violaceous pyramids and swollen cortex, ulcerative colitis was present. The brain was normal. Microscopically there was an acute tubular degenerative nephritis with marked congestion and the presence of calcification in the tubules.

#### COLLOIDAL GOLD

The number and variety of causes assigned to the mechanism of the colloidal gold reaction attest our lack of accurate knowledge regarding it. It has been shown (Weston quoted by Warwick and Nixon<sup>17</sup>) that the substance is dialyzable through membranes impermeable to albumins and is precipitated by ammonium sulphate, hence, a globulin. On the other hand, pathologic increase in albumin has been said by another observer to be the cause of the precipitation. Still other workers have regarded it as a physical phenomenon, probably of electrical nature.

From our colloidal gold readings, it appears that proteins per se, that is, albumin and globulin, do not produce precipitation of the colloidal gold suspension. Two outstanding cases, 8 and 9, show at once the presence of completely negative colloidal gold reactions with quantitative protein values of 200 and 188 mg, respectively.

On the whole, a characteristic change in the colloidal gold curve of the cerebrospinal fluid in nephritis is not apparent.

The dearth of autopsy material in this article is greatly regretted. Clinical work can never have the value of clinicopathologic observations. We feel, however, that the cases described in this article are for the most part clear-cut clinical pictures recognized by all as nephritis.

<sup>17</sup> Warwick and Nixon. Study of Colloidal Gold Reaction and Its Clinical Interpretation, Arch Int Med 25 119 (Feb) 1920.

## CONCLUSIONS

1 Cerebrospinal fluid and blood studies were made on cases of nephritis with and without uremic manifestations

2 The cerebrospinal fluid in chronic nephritis shows the following

(a) The cerebrospinal fluid is clear This was true in all of our cases except one, in which the fluid had a faint yellow-green tinge Pressure, as judged by the initial spurt and rapidity of flow, is increased

(b) The cell count varies from 2 to 16 per cubic millimeter, these cells are essentially all lymphocytes With the exception of one case with a polymorphonuclear count of 50 per cent, this was true in the series studied The presence of uremia has no relation to the cell count

(c) The nonprotein nitrogen of the cerebrospinal fluid is increased and is higher than the normal proportion in relation to the blood nonprotein nitrogen The ratio,  $\frac{\text{Cerebrospinal nonprotein nitrogen}}{\text{Blood nonprotein nitrogen}}$ , normally 46 per cent, rises to 80 per cent in the presence of nitrogen retention

(d) The chlorides are not generally increased The figures for the cases with edema are essentially the same as for those without edema In fluids taken post mortem the chlorides are exceptionally high

(e) There is a definite increase in albumin and globulin in cases of chronic nephritis, the highest figures are obtained in the presence of uremia When the protein is more than 100 mg per one hundred cubic centimeters, the prognosis is grave

(f) The ratio,  $\frac{\text{Blood sugar}}{\text{Cerebrospinal fluid sugar}}$ , is higher in chronic nephritis, averaging 74.3 for eleven of our cases Over 50 per cent of the cases gave a higher cerebrospinal fluid sugar than normal In the presence of uremia the average figure obtained is higher than in the absence of uremia

3 In the absence of uremic manifestations, the cerebrospinal fluid in acute nephritis is essentially normal in all respects In the presence of uremic symptoms, the protein content rises

4 In the acute nephritis of mercuric chloride poisoning, the cerebrospinal fluid resembles closely that seen in chronic nephritis

5 Apparently there is not a characteristic change in the colloidal gold curve of the cerebrospinal fluid in nephritis The amount of protein per se, that is, albumin and globulin, bears no direct relation to precipitation of the colloidal gold suspension

# THE TOXIC ACTION OF CYSTINE ON THE KIDNEY

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It has been shown by Newburgh and his collaborators<sup>1</sup> that diets high in protein are injurious to the kidneys. In the attempt to explain the mechanism of this injury it was found that the intravenous injection of certain amino-acids into animals gave positive results, and that the injury produced was obtained by a single dose or, at most, by the administration of a few doses of the amino-acid in question.

These acute lesions caused by large intravenous doses suggest the possibility that the introduction of the amino-acid into the body in small doses with the food over a long period of time might also produce injury. This investigation was devised to obtain an answer to this question.

Cystine was selected as the amino-acid to be studied in this regard for several reasons. 1. When it is injected intravenously a severe lesion is produced. 2. Cystine is an essential amino-acid as Mendel has shown. He demonstrated this fact by feeding a cystine-poor ration obtained by using casein as the protein and by restricting it to 8 per cent of the diet. On this diet, growth is limited by the small amount of cystine present. Mendel has further shown that the addition of 0.25 per cent cystine to this diet promotes growth. It is therefore possible to determine by graded additions of cystine to such a casein diet at what level (if any) beyond the requirement for growth the cystine of the diet may become harmful to the kidneys. 3. Lignac<sup>4</sup> has reported

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<sup>1</sup> From the Department of Internal Medicine, University of Michigan Medical School.

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1. Newburgh, L. H. Production of Bright's Disease by Feeding High Protein Diets, *Arch. Int. Med.* **24** 259 (Oct.) 1919. Newburgh, L. H., and Clarkson, Sarah. Renal Injury Produced in Rabbits by Diets Containing Meat, *Arch. Int. Med.* **32** 850 (Dec.) 1923. Newburgh, L. H., Marsh, P. L., Clarkson, Sarah, and Curtis, A. C. The Dietetic Factor in the Etiology of Chronic Nephritis, *J. A. M. A.* **85** 1703 (Nov. 28) 1925.

2. Newburgh, L. H., and Marsh, P. L. Renal Injuries by Amino-Acids, *Arch. Int. Med.* **36** 682 (Nov.) 1925.

3. Osborne, T. B., and Mendel, I. B. *J. Biol. Chem.* **17** 325, 1914, 20 351, 1915.

4. Lignac, G. O. E. *Krankheitsforschung* **2** 43 1925.

severe tubular injury in mice caused by the subcutaneous injection of a suspension of cystine. H. B. Lewis<sup>5</sup> has found that the introduction of cystine into the body of rabbits through the digestive tract is nephrotoxic when the doses are large. He introduced a suspension of cystine into stomachs of fasting rabbits by means of a tube. From 1 to 2 Gm of cystine per kilogram was introduced in this manner every second or third day. After a few such doses had been taken, the rabbits showed unmistakable signs of kidney injury. It is therefore clear that large amounts of cystine will injure the kidney when it is ingested, as well as when it is injected into the circulation, but the results which are obtained when a large amount of cystine is poured into the fasting stomach cannot be used as a measure of what will follow when an animal slowly eats cystine thoroughly mixed with the other constituents of a diet.

#### METHOD

In our experiment, white rats were used and were cared for according to the technic of Ferry<sup>6</sup>. All of the animals that were expected to eat the diet containing relatively the smaller amounts of cystine received it by replacement of the cornstarch either in a standard 18 per cent diet or in an 8 per cent casein diet. The animals that were fed from 25 to 20 per cent cystine received it as an addition to the standard 8 per cent casein diet. In addition, each rat daily received 0.05 Gm of yeast vitamin extract. The cystine used in the experiment was made in this laboratory from hair, by the standard method. The rats can be conveniently dealt with in three groups, *A*, *B* and *C*.

The rats in group *A* all received the basic diet of 18 per cent casein, containing in itself sufficient cystine for growth. Cystine was added to this diet to the extent of 0.5 per cent for two rats, 1.1 per cent for three rats and 2.2 per cent for two rats.

The rats in groups *B* and *C* all received the basic diet of 8 per cent casein. This diet contained too little cystine for growth.

Group *B* consisted of those rats that received from 25 to 20 per cent of the diet in the form of cystine for relatively short periods of time. Both adult and young rats were used.

Group *C* consisted of rats, each one of which was taken from its mother at the end of the first month of life, confined in an individual cage and given the appropriate diet. Twenty-five rats were used and separated into six groups: group 1, consisting of five rats, received the basic diet; group 2, consisting of four rats, received the basic diet plus 0.25 per cent cystine; group 3, consisting of four rats, received the basic diet plus 0.75 per cent cystine; group 4 received the basic diet plus 1 per cent cystine; group 5 received the basic diet plus 1.25 per cent cystine and group 6 received the basic diet plus 1.5 per cent cystine. All except three of the animals were fed according to this plan for approximately one year; one, from the sixth group, lived 284 days, and the other two from the first and the fifth groups, lived 306 and 283 days, respectively (table 1).

The weight of the rat and the weight of the food eaten were recorded each week. A twenty-four hour specimen of urine from each rat was examined for albumin and casts every second month throughout the period of observation. In addition to this, the urine obtained during the last two series of examinations was subjected to a quantitative, as well as to a qualitative, examination. For

5 Lewis, H. B. Metabolism of Sulphur, Effect of the Repeated Administration of Small Amounts of Cystine, *J. Biol. Chem.* **65** 187 (Aug.) 1925.

6 Ferry, Edna L. *J. Lab. & Clin. Med.* **5** 735 (Aug.) 1919-1920.

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[illegible][illegible]

\* The baby but continued 8 per cent of protein  
† Died of meningitis day after this examination

this purpose the amount of albumin contained in a twenty-four hour specimen was measured by the method of Folin,<sup>7</sup> and the total number of casts in the specimen was counted according to the technic of Addis.<sup>8</sup>

When a specimen of urine was to be collected, the rat was placed in a container the general shape of the individual rat cages, the walls of which were made of a sheet of galvanized iron instead of wire mesh. At the bottom of the cage, a horizontal flange projecting inward 1 inch supported a 10-inch funnel. Resting on the funnel was a floor made of galvanized iron wire screening of one-half inch mesh. Immediately below the stem of the funnel, a second, small, funnel, supported by a convenient clamp, contained an egg-shaped bulb which was held away from the sides of this smaller funnel by several glass prongs projecting from the side of the bulb. This smaller funnel drained into a flask containing a crystal of thymol. The rat was confined in this cage by the usual type of weighted screen lid.

Many of the animals in group *B* that received the highest diets died in a few days, the others were killed by a blow on the head. In both cases, the tissues were preserved in formaldehyde for subsequent histologic study.

The animals in group *C* that lived to the end of the experimental period were killed by a blow on the head, and the organs were inspected and preserved in formaldehyde for subsequent study. Tissues were not preserved from the animals that died during the experiment. The weight of both kidneys was obtained within a few minutes after death.

#### RESULTS OF THE EXPERIMENT

*Group A*—These experiments show the effect of the addition of cystine to a diet in itself adequate for growth, that is one which contains sufficient preformed cystine as measured in terms of growth.

This basic diet has been fed by us to eight rats for eleven months and to three rats for seventeen months both before and during the time when the cystine diets were being used. All the rats, both control and experimental, have been housed in a single large room under conditions which were identical for all with the exception of the diet. The urine of the control rats that received the diet to which cystine had not been added was examined every other month for the presence of albumin and casts. In addition to this, we have six quantitative determinations of the amount of albumin and the number of casts, if any, after 240 and 450 days of the diet. In not a single instance were any casts found. On the other hand, the tests for albumin were sometimes positive to a slight degree. Other investigators have also noted the irregular occurrence of some substance which is precipitated by heat and acetic acid, and it has been questioned whether this material is albumin in the pathologic sense or whether it is merely an unusually large amount of the precipitable substance normally present in the rat's urine. We have not made any attempt to answer this question, but have considered only heavy albuminurias as evidence of disease. Albuminurias of less than 0.1 per cent do not appear to have a pathologic significance.

<sup>7</sup> Folin J. B. C. 18 283, 1914

<sup>8</sup> Addis Thomas A Clinical Classification of Bright's Diseases J. A. M. A 85 163-167 (July) 1925

The addition of as little as 0.5 per cent of cystine to this diet produces evidence of renal injury after the diet has been ingested continuously for four or five months. The three rats that ate the diet containing 1.1 per cent cystine voided urine in which casts were found in small numbers as early as the second month. The number of casts in these urines slowly increased as the feeding continued. The microscopic examination of the kidneys of these animals revealed well marked tubular injury. One of them, rat 129, that was permitted to eat the diet for more than a year voided grossly hemorrhagic urine at the end of the experimental period, and was killed at this time that we might examine the genito-urinary tract. Sources of hemorrhage other than the kidney were not seen. The two animals whose diet contained 2.2 per cent of cystine both voided abnormal urine within the first month. The kidneys of the animal that died had undergone postmortem changes before preservation. The kidneys of the one that was killed after six months showed the same type of injury in general as that seen in the rats that received half this amount of cystine.

Table 3 makes it clear that the onset of injury is roughly proportional to the concentration of cystine in the diet as indicated by the first appearance of casts. Glomerular injury was not seen in any of the sections.

*Group B*—These animals received a basic diet the total protein of which was 8 per cent in the form of casein. Such a diet contains so little preformed cystine when compared to the amount added to the diets fed all these animals that the amount of it in the basic diet may be ignored. The injury may, therefore, be directly compared with the amount of added cystine.

Inspection of table 2 shows that the diet containing 20 per cent of cystine acted as a violent poison. Rat 213 shows how extensive an injury may be obtained within a period of only several days on a diet containing 20 per cent of cystine. The rats that ate the diet containing 10 per cent of cystine also reacted in a way that suggested the effect of a powerful poison, since three out of four were dead in a week. When the diet contained only 5 per cent of cystine the animals were able to survive at least two weeks, at which time they were killed because they were apparently within a few hours of death. A further reduction of cystine to 3.75 per cent of the diet permits continued, but very slow, growth.

The urine column of table 2 shows that within a few hours after the first ingestion highly abnormal urine is obtained from a rat eating the diet highest in cystine content. The 10 per cent cystine diet caused the urinary evidence of injury to appear on the second day. When the diet contains 5 per cent of cystine, it takes approximately twice as long to affect the rat as when 10 per cent of cystine is fed. The urinary

response is delayed a little further when cystine is 3.75 per cent of the diet, and finally, fifteen days elapse before casts appear in the urine when the animal eats the diet containing 2.5 per cent of cystine.

The degree of abnormality seen at autopsy and in the microscopic examination of the kidneys was roughly proportional to the cystine content of the diet.

Figures 1 and 2 show the extent and degree of tubular injury caused by the ingestion for two weeks of a diet containing 5 per cent of

TABLE 2—*Effect of Large, Increasing Amounts of Cystine on Growth and on the kidney*

Cystine in Diet, Per cent	Rat No.	Initial Weight	Final Weight	Cystine Eaten per Kg per Day	Duration Days	Urine	Results
20	212	69	62	4.6	2	Much albumin and many casts after 24 hours	Animal died, no tissues saved
	213	95	78	4.1	3	Much albumin and many casts, fat droplets on third day	Widespread tubular necrosis, many casts
10	210	86	68	3.9	7	Much albumin and many casts, second day	Animal died, no tissues saved
	211	84	70	3.1	5	Albumin, casts, red blood cells on fourth day	Animal died, no tissues saved
	221	197	185	1.7	3	Much albumin and many casts on second day	Animal died, no tissues saved
	222	122	115	2.5	3	Albumin casts and blood cells on second day	Uniform complete necrosis of tubules, pyknotic nuclei
5	214	65	52	2.6	13	Albumin and casts on fourth day	Figs 1 and 2
	215	76	50	2.1	14	Much albumin and many casts on fifth day	
3.75	230	124	131	1.6	297	All animals of this group had albumin and casts on the sixth day; these abnormalities persisted to the end	Cloudy swelling of cortex and casts
	231	119	132	1.6	280	Albumin and a few casts on the fifteenth day; these observations continued to the end	One large circumscribed area of fibrosis, the remainder showed cloudy swelling
2.5	225	56	92	1.5	280		

cystine. It should be emphasized that the ingestion of as small an amount as 5 per cent of cystine did produce this widespread necrosis in two weeks.

*Group C*—This particular part of the investigation was planned to determine how much cystine, beyond the requirement for growth, could be ingested with impunity. In order to answer this question it is necessary to know the cystine content of casein. Two different methods have been employed to obtain this information. The older one<sup>9</sup> deter-

<sup>9</sup> Van Slyke, D. J. *Biol. Chem.* **16**: 531, 1913-1914. Jones, D. B., Gersdorff, C. E. F., and Moeller, O. The Tryptophane and Cystine Content of Various Proteins, *ibid.* **62**: 183 (Nov.) 1924.



Fig 1—A complete section of this kidney is presented to show the pale band located in the lower part of the cortex of the kidney of rat 214 (table 2) which received 5 per cent of cystine in its diet for thirteen days. This band extends around the kidney from pole to pole.

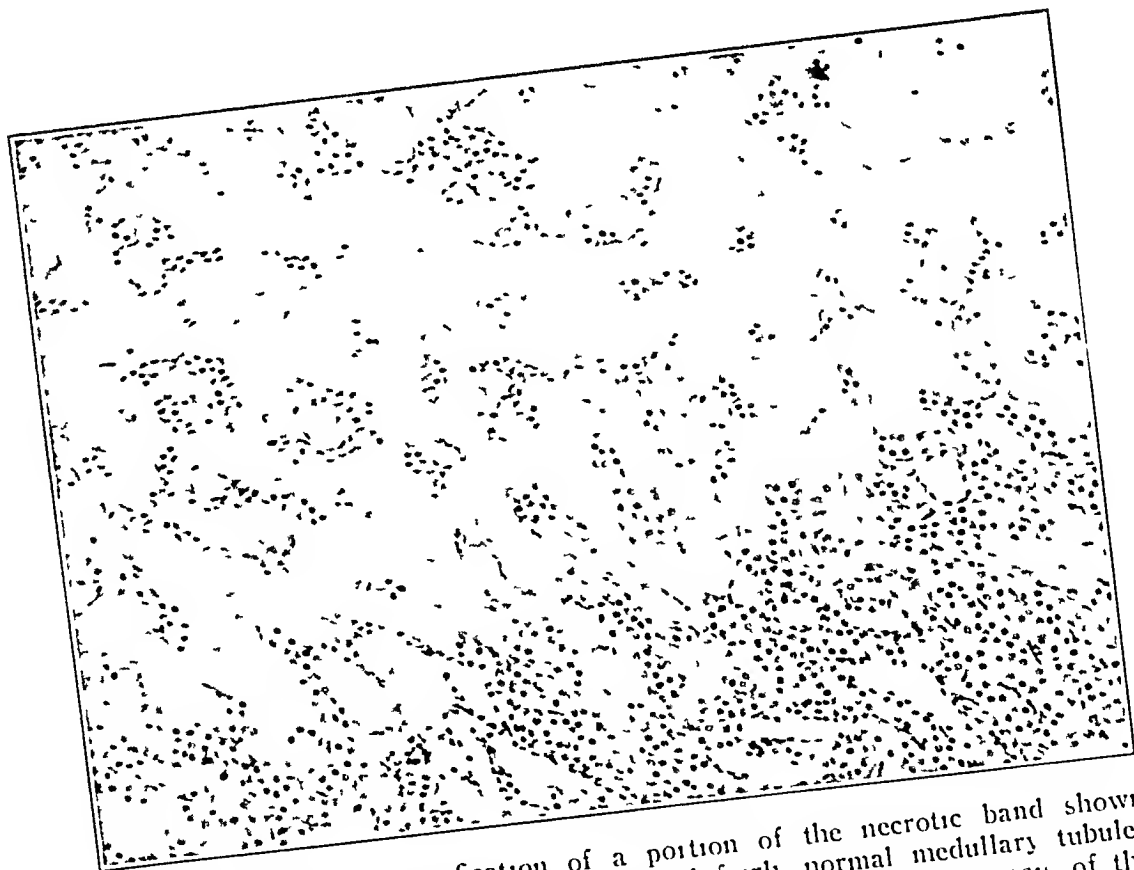


Fig 2—Greater magnification of a portion of the necrotic band shown in figure 1. In the lower part of the field fairly normal medullary tubules are seen. The remainder of the field shows almost complete necrosis of the cortex.

mines the cystine by chemical analysis, and the best data indicate that 0.26 per cent of casein can be recovered as cystine. More recently, Sherman<sup>10</sup> determined how much cystine or cystine equivalents are contained in casein, and he concluded that these materials form from 1.3 to 2.5 per cent of it. In what follows we will first calculate the data secured from our feeding experiments, according to the cystine content of casein obtained by chemical analysis, and later recalculate the data, using the results of Sherman's biologic method.

Table 3 presents the total gain in weight for each of the groups in this division. This table shows how poor the growth is on the basic diet, how it is improved by the first addition of cystine, how further improvement is not obtained from larger amounts of cystine, and finally, how further improvement is obtained when the protein of the diet is 18 per cent casein.

Chemical analysis indicates that casein contains 0.26 per cent of cystine. Accordingly, when the protein of the diet is 18 per cent in the form of casein, such a diet will contain 0.47 per cent of cystine. This amount permits good growth. On the other hand, diets containing only 8 per cent of casein with 0.21 per cent of cystine will not permit good growth. Since rats on this type of diet receive a yeast tablet daily it is necessary to add the cystine content of this material to the calculation.<sup>11</sup> When this is done, it is found that the minimal requirement is approximately 0.06 per cent cystine. The total cystine ingestion on an 8 per cent casein diet is approximately 0.035 per cent.

Table 1 shows that the addition of 0.25 per cent cystine was, as might have been expected, enough to give as good growth as did any further additions, and that this diet, containing approximately five times the minimal cystine requirement, does not cause the animal to ingest enough cystine to injure the kidneys, as determined by urinalysis. When, however, the diet contains 0.75 per cent of cystine, which is approximately thirteen times the requirement, evidence of renal injury in the form of casts begins to appear after five months. The diets containing further small additions of cystine up to and including 1.5 per cent give additional evidence of renal injury, which tends to appear earlier in proportion to the increasing level of cystine.

Our preliminary experiments, however, showed that the addition of 0.5 per cent of cystine to an 18 per cent diet was injurious. The cystine ingested at this level is roughly ten times the minimal requirement. Our data further indicate that the addition of cystine in amounts five times the minimal requirement is harmless, while on the other hand the addition of ten times the required amount of cystine produced evidence of

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10 Sherman, H. C., and Woods, Ella. *J. Biol. Chem.* **66**: 29 (Nov.) 1925.

11 McGinty, D. A., Lewis, H. B., and Marvel, C. S. *J. Biol. Chem.* **62**: 75 (Nov.) 1924 (M. L. Long's Analysis).

TABLE 3—*The Relation Between the Amount of Cystine in the Diet and the Kidney Injury*

Rat No	Sex*	Cystine per Cent Added to Diet†	Initial Weight Gm	Days on Diet												Outcome
				1 to 10		10 to 20		20 to 30		30 to 40		40 to 50		50 to 60		
				Albu min	Cyst-s min	Albu min	Cyst-s min	Albu min	Cyst-s min	Albu min	Cyst-s min	Albu min	Cyst-s min	Albu min	Cyst-s min	
125	♀	2.2	214	+	+	+	+	+	+	+	+	+	+	+	Died after 140 days on diet; no tissues saved	
126	♀	2.2	88	+	+	+	+	+	+	+	+	+	+	+	Killed after 1st days on diet; irregular necrosis of tubules; numerous casts	
127	♀	1.1	246	0	0	0	+	+	+	+	+	+	+	+	Killed after 170 days on diet; some tubules are necrotic and take a violet stain typical of calcium in my casts	
128	♂	1.1	285	0	0	+	+	+	+	+	+	+	+	+	Killed after 170 days on diet; tubules of cortex show minor degree of necrosis; many casts	
129	♂	1.1	25	0	0	+	+	+	0	+	+	+	+	+	Killed after 71 days on diet; diffuse hemorrhage in addition to changes described for rat 127	
130	♀	0.5	77	0	0	0	0	+	+	0	+	+	+	+	Died after 270 days on diet; no tissues saved	
131	♀	0.5	88	0	0	0	+	0	+	+	+	+	+	+	Killed after 180 days on diet; minor degree of cloudy swelling and a few casts	

\* In the table ♀ indicates female ♂ male

† The basic diet contained 18 per cent of protein as casein

injury (table 4) The information at hand does not permit us to determine at what point between these two levels (that is, from five to ten times the requirement) the toxic effects first occur

Sherman's biologic assay indicates that casein yields not less than 1.3 per cent cystine and not more than 2.5 per cent cystine In order to simplify the calculations, we will use the average figure of 2 per cent and will not add the cystine content of the vitamin tablet to the total yield of the diet, because the tablet contains a negligible amount of cystine

By Sherman's method, it is found that the 18 per cent casein diet which gives good growth contains 0.36 per cent of cystine, and that the 8 per cent casein diet on which rats do not grow well yields 0.16 per cent cystine Our data show that the addition of 0.25 per cent cystine to this 8 per cent diet is harmless Such rats ingest a diet containing 0.41 per cent cystine On the other hand, an 18 per cent casein diet to which 0.5 per cent of cystine is added, making a total cystine percentage

TABLE 4—*Effects of Increasing Amounts of Cystine on Growth and on the General Condition of the Rat*

Chemical Analysis		Biologic Assay		Effect
Amount in Diet, per Cent	Times Requirement	Amount in Diet per Cent	Times Requirement	
0.0035		0.0160		Poor growth
0.0060	0	0.0360	0	Requirement for growth
0.0285	5	0.0410	1.1	Harmless
0.0560	10	0.0860	2.5	Mildly harmful growth occurs
1.160	17	1.460	4	Moderately harmful, growth occurs
3.800	63	3.910	11	Markedly harmful, growth inhibited
5.000	83	5.000	14	Severely harmful death in two weeks
10.000	165	10.000	28	Violently harmful death in five days

of 0.86, is harmful Hence, on the basis of the biologic assay, it is found that diets containing roughly two and one-half times the requirement are harmful (table 4)

It might be questioned whether the cystine made in the laboratory by hydrolysis gives any information regarding the effect of the preformed cystine as it occurs in the food, since laboratory manipulations might convert a harmless material into a harmful one, even though the hypothetical difference is not yet detectable by the most refined chemical methods It is easy to show however, that the cystine we have used is not harmful in the qualitative sense, for the addition of it to a diet containing too little cystine to permit good growth greatly increases the growth promoting quality of the diet

#### SUMMARY

1. An 8 per cent casein diet which contains (a) 0.021 per cent cystine by chemical analysis, or (b) 0.16 per cent cystine by a biologic assay, does not permit good growth

2 An 18 per cent casein diet which contains (a) 0.047 per cent cystine by chemical analysis, or (b) 0.36 per cent cystine by a biologic assay does permit good growth

3 The addition of 0.25 per cent of cystine to an 8 per cent casein diet is harmless but the addition of 0.5 per cent cystine to an 18 per cent casein diet is mildly harmful. Accordingly cystine in the diet becomes harmful when it is 2.5 or ten times the requirement, depending on whether the preformed cystine of the basic diet is determined by biologic assay or by chemical analysis

The evidence of renal injury increases as the level of the cystine in the diet is raised. Thus levels ranging around 1.5 per cent of cystine in the diet produce necrosis of the renal tubules in the course of a year. Four per cent of cystine is sufficiently injurious to interfere with the growth of young animals in addition to producing the injury obtained in lower levels. When 5 per cent of cystine is added to the diet the effect begins to resemble that of a powerful poison. Animals that are fed such a diet succumb in several weeks. A diet containing 10 per cent of cystine kills in a few days and when a fifth of the diet is cystine death follows in two or three days. These large amounts of cystine cause diffuse hemorrhagic necrosis of the renal parenchyma.

# THE TOXIC ACTION OF CYSTINE ON THE LIVER OF THE ALBINO RAT<sup>1</sup>

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AND  
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While performing the postmortem examination of rats described in a preceding article which deals with the nephrotoxic action of ingested cystine, it was found that liver injury was commonly present in those rats that had ingested the diets containing 0.75 per cent or more of cystine. The livers of those rats that received the largest amounts of cystine were much darker than normal and suggested the color of fresh blood clot, whereas in the rats that had been fed small amounts of cystine, an outstanding gross injury was not detected.

## *Effect on Rats' Livers of Increasing Amounts of Cystine in Diminishing Intervals of Time*

Rat Number	Duration of Feeding Days	Cystine in Diet per Cent	Injury
147	409	0.75	Numerous irregular areas of interlobular necrosis
141	409	1.50	Marked degree of constant interlobular necrosis, cells of these areas showed indefinite outlines and pyknotic nuclei, the remainder of the liver tissue showed this same change in a minor degree
251	104	4.00	The tissue showed a generalized fatty infiltration and necrosis most marked about the portal veins
222	4	10.00	Large patches of hemorrhagic necrosis involving especially those areas about the portal veins, remainder of liver tissue showed a marked necrosis
213	4	20.00	Only a small wedge of partially normal cells remained the remainder of the tissue had been destroyed by hemorrhagic necrosis involving both interlobular and intra lobular regions

On microscopic examination it was found that even the addition of 0.75 per cent of cystine to an 8 per cent casein diet gave evidence of well marked injury. Further microscopic study indicated that the degree and extent of the injury was roughly proportional to the amount of cystine in the diet (table 1).

The character of the lesion is described in detail in the accompanying protocols.

## EXPERIMENTS ON RATS

RAT 147—This rat, a female, aged 1 month, was placed on a diet of casein, 8 per cent to which 0.75 per cent cystine had been added by a replacement of an equal amount of cornstarch in the diet. Its weight was 48 Gm. It remained

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<sup>1</sup> Aid for this investigation was received from the Ella Sachs Paltz Foundation for the Advancement of Scientific Investigation.

on this diet for twelve months, at which time it was killed. The antemortem weight was 172 Gm.

*Necropsy*—The kidneys weighed 164 Gm and were dark, but did not show other gross abnormalities. The surface of the liver showed many small dark areas which suggested hemorrhage. Both the liver and the kidneys were preserved in formaldehyde for histologic study. The other organs did not present any abnormalities.

Microscopic examination of the liver showed numerous patchy interlobular areas of injury. The cells of these regions were necrotic, and had nuclei which were both swollen and pyknotic. These areas stain poorly. Intervening areas of liver tissue were normal (fig 1).

RAT 141—This rat, a male, aged 1 month, was placed on a diet of 8 per cent casein to which 1.5 per cent cystine had been added by replacement in the diet, of an equal amount of cornstarch. It was killed at the end of one year for examination of its tissues. Its weight at this time was 170 Gm.

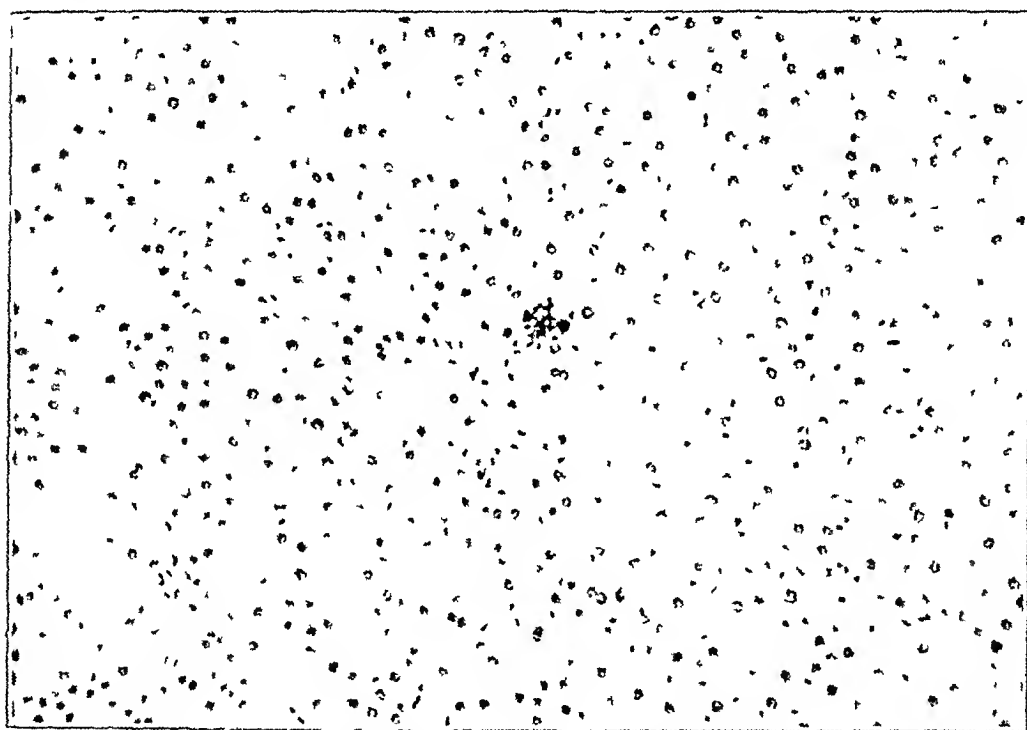


Fig 1 (rat 147)—Circumscribed areas of moderate injury caused by the ingestion of 2.5 times the minimal requirement of cystine for 409 days.

*Necropsy*—The kidneys of this animal were dark chocolate color but did not show other abnormalities. Their weight was 156 Gm. The liver was also unusually dark and had numerous small areas in its substance resembling hemorrhage. A piece of the liver and both kidneys were preserved in formaldehyde for subsequent study.

Microscopically, the liver showed a marked constant interlobular necrosis. The cells of these areas were vacuolated, and the small amount of granular cytoplasm remaining took the stain poorly. The poorly stained nuclei were irregular in size, and showed vesicular and pyknotic forms. The remainder of the liver tissue showed this same change in a minor degree (fig 2).

RAT 251—A male, weighing 36 Gm, was placed on a diet which contained 15 per cent of protein in the form of dried, powdered, lean beef, to which 4 per cent cystine had been added by replacement of an equal amount of cornstarch. Four weeks later urinalysis showed numerous granular casts and much albumin. These abnormalities persisted until the rat's death. At the end of one hundred and four days the animal was killed. Its weight at this time was 203 Gm.

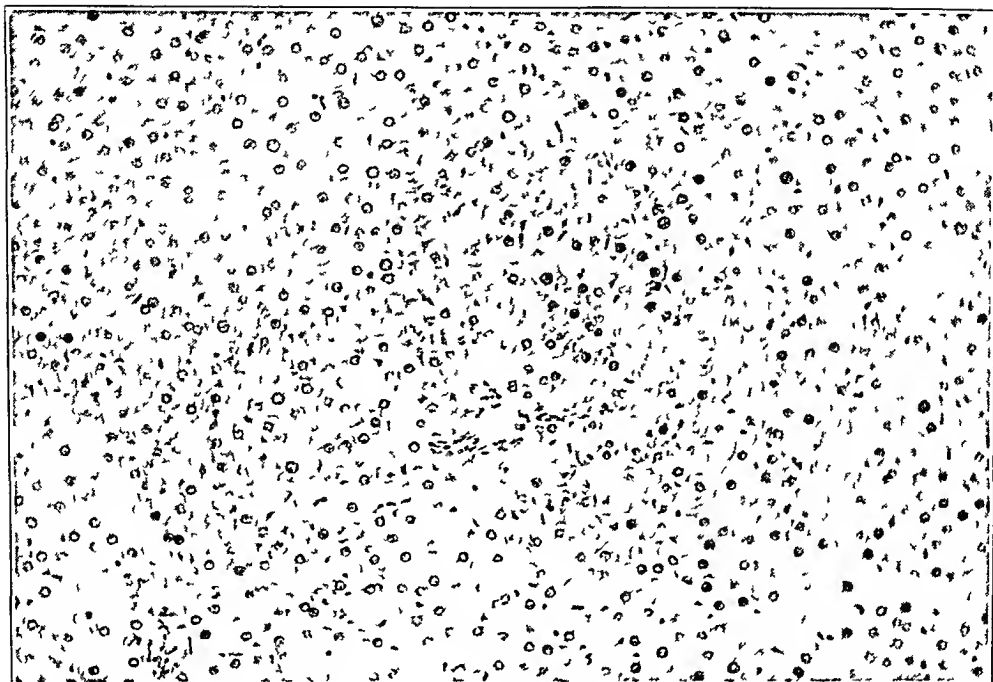


Fig 2 (rat 141) —Well marked interlobular injury caused by the ingestion of five times the minimal requirement of cystine for 409 days

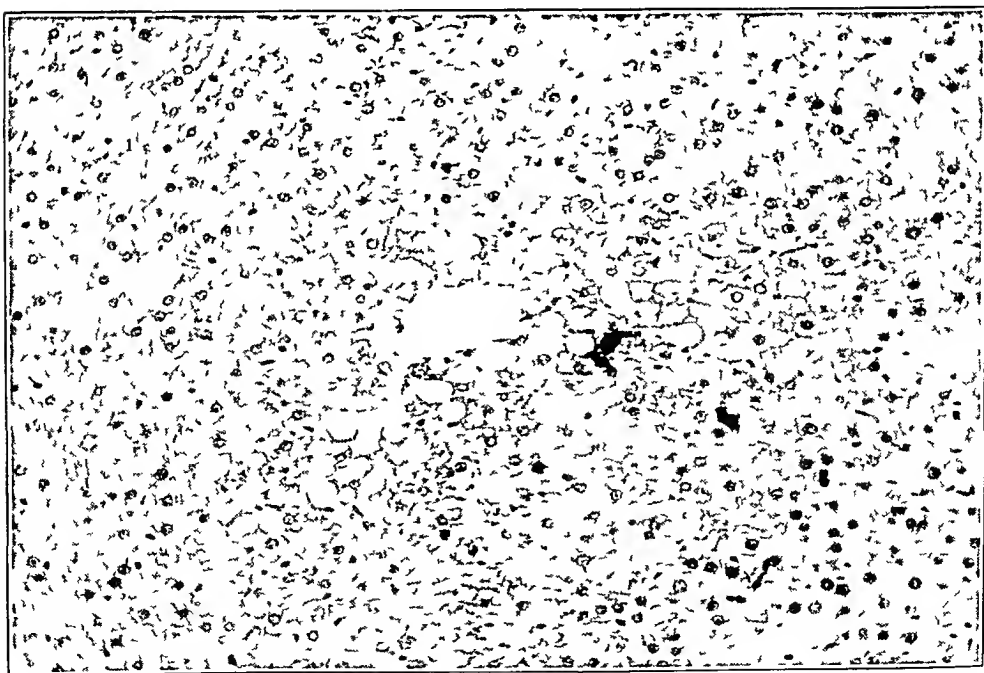


Fig 3 (rat 251) —Widespread severe cellular injury caused by the ingestion of twelve times the minimal requirement of cystine for 104 days

*Necropsy*—The kidneys of this animal were soft and dark, and showed some subcapsular hemorrhage. The liver was dark and structureless. On section, blood welled from its substance, leaving an irregular surface, caused by the presence of many flat yellow nodules. The urine from the bladder was loaded with granular casts. The other organs and tissues appeared normal.

Microscopically the liver showed a generalized, fatty infiltration and necrosis, most marked about the portal veins. The cell substance was granular and pale. The nuclei were pale in some areas, pyknotic in others and absent in still others. No region had escaped injury. A small amount of cell protoplasm remained, and fat pervaded the whole tissue (fig 3).

RAT 222—A male weighing 122 Gm, was put on a casen, 8 per cent, diet to which 10 per cent cystine had been added, on Dec 7, 1925. At this time its urine was normal. On Dec 9 1926 5,400 casts were counted in a twenty-four hour specimen of urine. On December 10 the animal was sick. It seemed near death and accordingly was killed. Its weight at this time was 115 Gm.

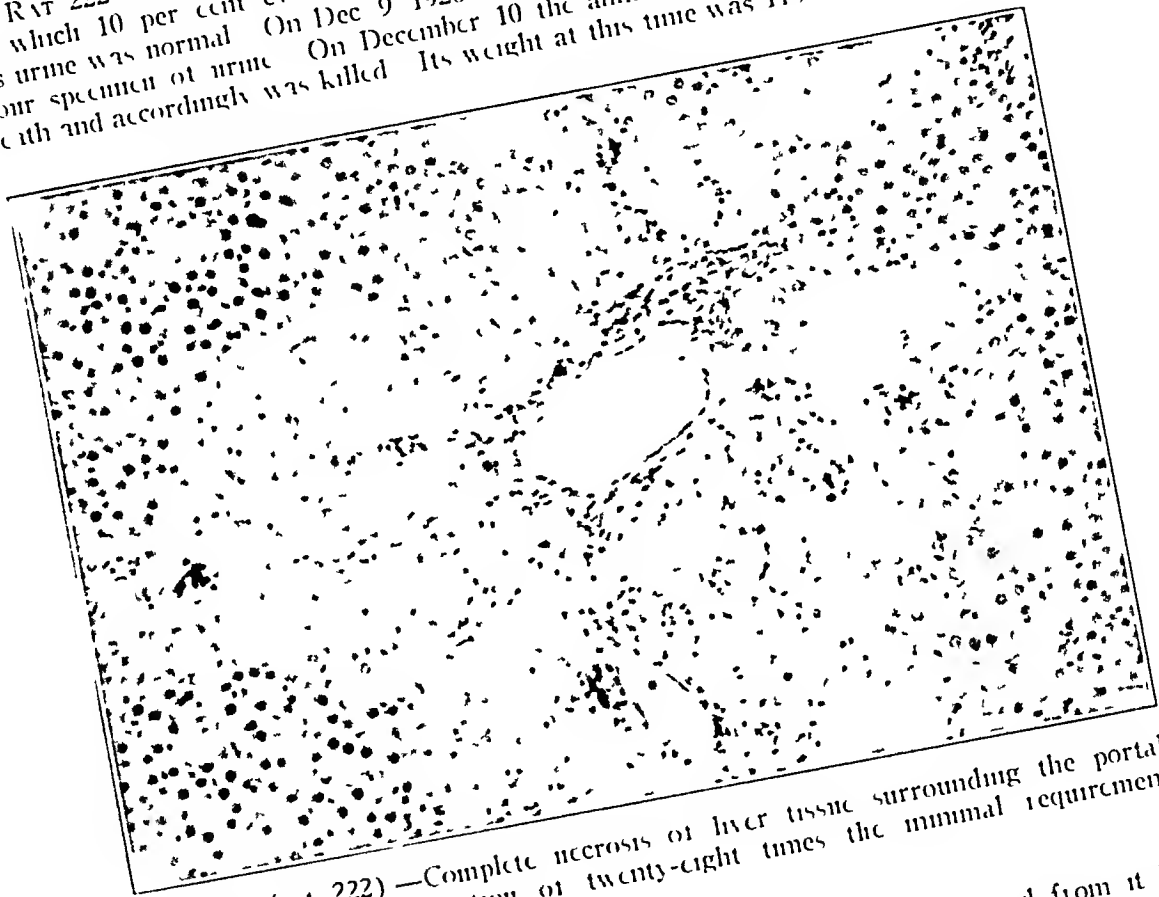


Fig 4 (rat 222)—Complete necrosis of liver tissue surrounding the portal vein caused by the ingestion of twenty-eight times the minimal requirement of cystine for four days.

*Necropsy*—The bladder was distended and a specimen removed from it by means of a capillary pipet was loaded with red blood cells. The kidneys were mottled with small hemorrhages. The liver presented the same appearance as already described in the protocol of rat 251.

Microscopically the liver showed large patches of hemorrhagic necrosis involving especially the areas about the portal veins. These regions were filled with red blood cells which had entirely replaced the parenchyma. The remainder of the liver showed a severe necrosis with faint cell boundaries and irregular pyknotic nuclei (fig 4).

RAT 213—On Nov 17, 1925, a female, weighing 85 Gm, was put on a casen, 8 per cent, diet to which 20 per cent cystine had been added. Its urine at this time was normal. On Nov 20, 1925, a specimen of urine was loaded with granular casts and contained albumin. On November 21, the animal appeared sick. Its urine was markedly positive for albumin and had numerous granular casts.

The urine was bright yellow and when stained with scarlet red was positive for fat. The animal weighed 78 Gm. It was killed on this date.

*Necropsy*—The kidneys were dark, and subcapsular hemorrhage was evident throughout their surface. On section they were wet and congested. The liver was dark and showed massive hemorrhagic areas which emptied like sinuses when sectioned, leaving an irregular pale yellow surface resembling the livers of rats 251 and 222.

Microscopically, the liver showed a massive hemorrhagic necrosis with only a small wedge of partially normal liver tissue left. In the involved area, cells other than red blood corpuscles were not present. The small wedge of partially normal liver tissue also showed a severe degree of necrosis (fig 5).

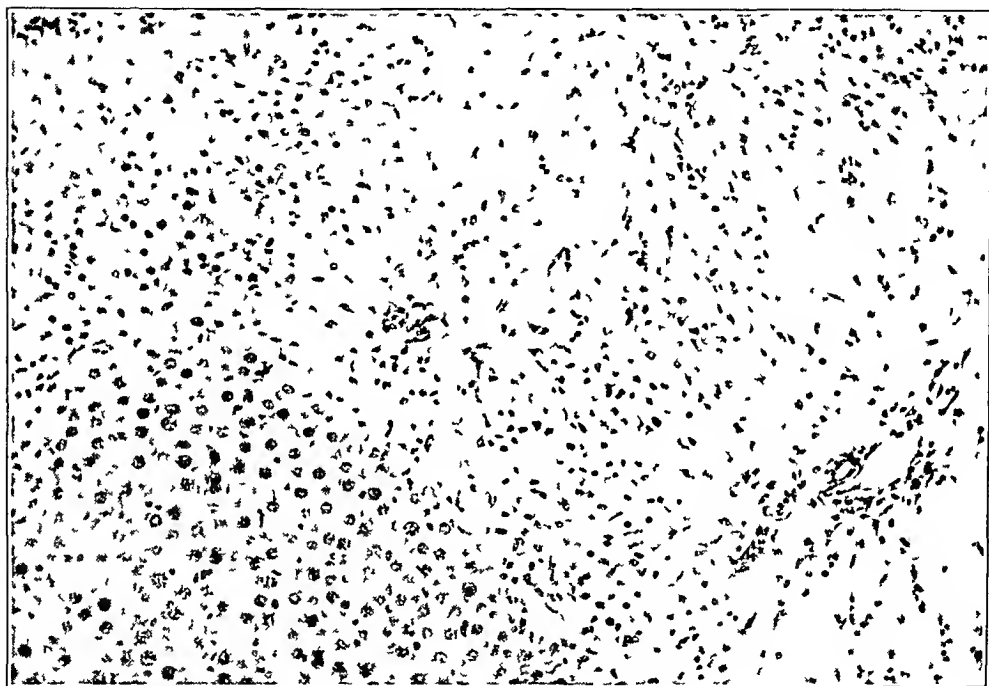


Fig 5 (rat 213) —Complete interlobular and intralobular necrosis of the liver caused by the ingestion of fifty-six times the minimal requirement of cystine for four days.

#### SUMMARY

The addition of so little as 0.75 per cent of cystine to an 8 per cent casein diet produces slowly occurring interlobular necrosis of the liver. According to the recently published biologic assay of the cystine content of casein,<sup>1</sup> such a diet contains about 2.5 times the cystine requirement for growth.

Further increases of cystine cause progressively greater injury in diminishing intervals of time.

The presence of 20 per cent of cystine in the diet has caused almost complete necrosis of the liver in four days.

<sup>1</sup> Sherman, H. C. and Woods, Ella. Determination of Cystine by Means of Feeding Experiments. *J. Biol. Chem.* 66: 29 (Nov.) 1925.

# WAR GASES AND TUBERCULOSIS

## AN EXPERIMENTAL STUDY

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When toxic gases were introduced as a new weapon of warfare, it was the natural reaction of the laity, as well as of the medical profession, to believe that their effects on the lungs would cause a predisposition to pulmonary tuberculosis. This early conclusion, hastily arrived at before there were any facts available for affirming or denying it, has remained largely fixed in the minds of the laity and also in the minds of a considerable number of physicians. But what are the facts? What have the years during and since the war taught us of the relationship between the war gases and tuberculosis?

Information concerning this question can be gained from two sources: clinical experience, and laboratory experiments. The clinical experiences of many men have been recorded, and include data on thousands of cases of persons who had been gassed. A brief summary of these records will be given below. Except for one or two articles, the experimental side has been largely neglected. It was because of this fact that the present work was undertaken.

## HISTORICAL

The early and natural reaction of many physicians of renown was to assume that the effect of war gases on the lungs would be to cause the development of pulmonary tuberculosis, or at least to cause the reactivation of old healed lesions. Sergent and Agnel,<sup>1</sup> Sergent<sup>2</sup> and Mosny<sup>3</sup> expressed the opinion that gassing caused the reactivation of a latent tuberculosis. Sergent and Agnel reported a case of tuberculosis, rapidly progressive and fatal, following gassing with chlorine. However, by 1917 Sergent<sup>4</sup> had changed his mind about the relationship between gassing and tuberculosis and expressed the opinion that tuberculosis was a rare sequel to gassing. In 1925, in discussing the case which he reported with Agnel in 1915, he stated that the patient had

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1 Sergent, E, and Agnel, E. Note sur quelque effets cliniques des gaz asphyxiants, Bull et mem Soc m  d d h  p de Paris **39** 960 (Nov 5) 1915

2 Sergent, E. La tuberculose chez les soldats    la suite des traumatismes du thorax, Bull et mem Soc m  d d h  p de Paris **40** 1048 (June 30) 1916

3 Mosney, E. Le traumatisme et la tuberculose, Bull et m  m Soc med d h  p de Paris **40** 1062 (June 30) 1916

4 Sergent, E. Les suspects de tuberculose, Paris med (April 7) 1917, quoted by Roubier and Simonin

been under profound intoxication from the gas, and was left with albuminuria and attacks of recurring purpura<sup>5</sup> He also added that a short while before the war the soldier had suffered an attack of pulmonary congestion which lasted for three months, and in the course of which there had been several hemoptyses He thinks that, because of its general nature, the profound intoxication by the gas had the effect of rousing a tuberculosis still active, if not progressive

Reports before the war of a few isolated cases of pulmonary tuberculosis following prolonged professional exposure to various vapors undoubtedly had its effect on the early formation of opinion following the first gas attacks in 1915 As early as 1886, Poincaré<sup>6</sup> had listed a number of diseases caused by chlorine, and included among them caseous pneumonia In 1900, Renon and Latron<sup>7</sup> reported a case of tuberculosis following continuous exposure to chlorine gas in industry In 1910, Audry<sup>8</sup> reported a case of tuberculosis in a young chemist following prolonged exposure to the vapors of liquor formaldehydi Sergent refers to the case of Renon and Latron, and says that its effect on the formulation of opinion was that it tended to double the phthisiogenic rôle of the war gases

With the exception of the articles mentioned, only a few instances can be found in the literature in which the opinion is expressed that gassing predisposes to tuberculosis

Boinet<sup>9</sup> stated that the action of gas not only reactivates a latent tuberculosis, but also favors new infection with the tubercle bacillus

Simonin,<sup>10</sup> in 1920, quoted an unnamed German author who had stated that preexisting tuberculosis may be aggravated by the influence of gas

In 1918, Dumarest<sup>11</sup> reported a case of tuberculosis following gassing In 1920, he published another article<sup>12</sup> in which he disagreed with other opinions of the day and cited eleven cases of tuberculosis,

5 Sergent, E Les sequelles respiratoires des intoxications par le gaz de combat *Presse med* **33** 201 (Feb 14) 1925

6 Poincare Traite d'hygiene industrielle, Paris, 1886, p 79 Quoted by Renon and Latron

7 Renon, L, and Latron Intoxication professionnelle par les vapeurs de chlore, acue chlorique et tuberculose pulmonaire, *Bull et mem Soc med d hôp de Paris* **17** 436 (April 6) 1900

8 Audry, quoted by Euthymiou Etude sur la tuberculose pulmonaire post-traumatique, These de Lyon, 1918

9 Boinet Tuberculose pulmonaire consecutive aux traumatismes du thorax et aux gaz asphyxiants, *Marseille med*, March, 1919, quoted by Roubier

10 Simonin, C Contribution a l'etude du role etiological de l'intoxication par les gaz asphyxiants sur le developement de la tuberculose pulmonaire, These de Lyon, 1920

11 Dumarest La reforme des tuberculeux, *Bull med*, April 6, 1918 Quoted by Simonin

12 Dumarest, F Tuberculose et gaz asphyxiants, *Bull med* **34** 374 (April 21) 1920

either primary or reactivated, following gassing. He also referred to the experimental work of Celli and Guarnieri<sup>13</sup> published in 1886, and quoted them as finding that inoculation with tuberculosis by the air passages was more efficacious after preliminary irritation of these passages. A fuller account of the experiments of these workers will be given below.

In 1921, Sabshin<sup>14</sup> said that he had found 104 cases of chronic pulmonary tuberculosis in 1200 persons who had been gassed. This would make his percentage of tuberculosis following gassing 8.66 per cent, a much higher figure than has been reported by any one else. He failed to state, however, the history of his patients with regard to tuberculosis before being gassed, the history of gassing is vague, and he did not state on what the diagnosis of tuberculosis was made.

In 1921, Spicer<sup>15</sup> stated that he had "diagnosed a number of cases of tuberculosis two years after the gassing." Details are lacking, however, regarding the basis for the diagnosis.

Hazleton,<sup>16</sup> in 1923, stated that he thinks that coal gas escaping in bedrooms predisposes to tuberculosis. Undoubtedly it does, just as any other factor tending to lower the vitality of the patient might possibly be said to predispose to tuberculosis. He might just as well have said, however, that sleeping in a room with the windows down increases the incidence of tuberculosis.

In addition to the opinions of the foregoing authors, there are a number of isolated instances in which tuberculosis has occurred in persons who have been gassed. In 1916, Ménétrier<sup>17</sup> and Martinez reported the case of a person previously robust who developed phthisis after intoxication by gas. The patient died nine months after gassing. Autopsy showed cavities and tuberculous pneumonia. There were no calcified nodules.

In 1917, Tapie<sup>18</sup> reported the case of a person previously robust, who died from acute tuberculous bronchopneumonia twenty-five days after gassing.

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13 Celli, A., and Guarnieri, E. Ancora intorno alla profilassi della tubercolosi, *Atti d. r. Accad. med. di Roma* **2** 87, 1886.

14 Sabshin, Z. I. Chronic Effects of War Gassing, Notes on the Examinations of 200 Cases, *New York M. J.* **114** 232 (Aug. 17) 1921.

15 Spicer, F. W. The Relation of Chronic Gas Poisoning (Warfare) of the Lungs to Pulmonary Tuberculosis, *Minnesota Med.* **3** 573 (Dec.) 1920.

16 Hazleton, E. B. Carbon Monoxide as a Predisposing Cause of Pulmonary Tuberculosis, *Brit. M. J.* **2** 763 (Oct. 27) 1923.

17 Ménétrier and Martinez. Phthisie pulmonaire consécutive à l'inhalation de gaz asphyxiants, *Bull. et mem. Soc. med. d. hop. de Paris* **40** 1083 (July 7) 1916.

18 Tapie, J. Broncho-pneumonie tuberculeuse aigue consécutive à une inhalation de gaz asphyxiants, *Progres med.*, Oct. 20, 1917. Quoted by Sergent and Roubier.

Gouget,<sup>19</sup> in 1918, reported two cases. One was a reactivation of a latent tuberculosis, the other occurred in a patient without apparent tuberculous antecedents.

Tedeschi,<sup>20</sup> in 1918, reported one case of tuberculosis following gassing, and one case in which an old lesion was reactivated.

Challamel,<sup>21</sup> in 1919, reported a case similar to that of Tapie.

Engel,<sup>22</sup> in 1919, reported a case of acute primary tuberculosis of the larynx caused by gas. Simonin, in commenting on it, expressed the opinion that the case was probably one of reactivation of a preexisting tuberculous laryngitis. He cited the following case of Loeper's<sup>23</sup> to substantiate his views. A soldier died of bronchopneumonia after being overcome by mustard gas. Autopsy showed tuberculous laryngitis, but no tuberculosis of the lungs. There was a history of laryngeal disease for some months before the war.

Simonin,<sup>10</sup> in 1920, reported the following case. After the fatigue and exposure of thirty-one months of active infantry campaigning, a medical officer, recently taken from civil practice, was severely gassed with mustard gas and developed tuberculosis within the next few months.

During the same year, Roubier<sup>24</sup> also reported a case in which he thought that gassing undoubtedly caused the reaction of an old latent tuberculous lesion.

In the isolated observations just cited it does not necessarily follow that because tuberculosis developed after gassing the gassing was the cause of the tuberculosis. It is not a simple question of "post hoc ergo propter hoc." Sergeant<sup>5</sup> has recently pointed out that these cases are not necessarily sequelae, but that reactivation of pulmonary tuberculosis occurs conditioned by the profound general effect on the organism, they are not the consequence of a traumatic action occurring locally.

Of the opinions expressed in the literature concerning the relationship between tuberculosis and gassing, the overwhelming majority are to the effect that this relationship is remote. Elliott and Tovell,<sup>25</sup> in

19 Gouget. *Gaz irritants et tuberculose*, Paris med, March 2, 1918. Quoted by Sergeant.

20 Tedeschi, E. *Gas asfissianti e tubercolosi polmonare*, Riforma med **34** 2, 1918.

21 Challamel. *Blessures du poumon et tuberculose*, Paris med **9** 186 (March 1) 1919. Quoted by Sergeant.

22 Engel, R. *Les sequelles laryngees des gaz*, Gaz d hôp Paris **92** 697 (July 26) 1919.

23 Loeper. *Sclerose pulmonaire consecutive a l'yperite*, Progres med, 1917, no 10. Quoted by Simonin.

24 Roubier, C. *Intoxication par les gaz et tuberculose pulmonaire*, Gaz d hôp, Paris **93** 277 (Feb 21) 1920.

25 Elliott, J. H., and Tovell, H. M. *The Effects of Poisonous Gases as Observed in Returning Soldiers*, Internat J Surg **29** 383 (Dec) 1916.

1916 reported tuberculosis after gassing in three Canadian soldiers with a previous history of tuberculosis, arrested for some years. However, in 1917, Elliott,<sup>26</sup> who had had a large experience with returned soldiers, stated that "It is very gratifying to be able to state that gas does not seem to have stirred up tuberculosis to any great extent. It was feared that most of the cases would develop into tuberculosis, but very few have." Again in 1919, Elliott<sup>27</sup> stated that among soldiers with tuberculosis in the Canadian army he had found only a few who had become casualties through being gassed.

In 1916, Bernard<sup>28</sup> stated that the facts did not justify the conclusion that tuberculosis was caused by gas.

Gimbert<sup>29</sup> in 1917, fixed the percentage of cases of tuberculosis apparently caused by the action of gas at 3 per cent. In 1918,<sup>30</sup> in a statistical study made in a center of triage, he found in the previous history of the tuberculous subjects that only a minute proportion of them had been gassed (2.4 per cent).

Moricheau-Beauchamp<sup>31</sup> in 1,206 tuberculous subjects found that only three of them had been gassed.

Leon-Kindberg and Delherm<sup>32</sup> found that of 193 patients with tuberculosis only two had been gassed.

Bernard and Mantoux<sup>33</sup> found that of forty-six patients who had been gassed, only one had tuberculosis, and concluded that the inhalation of gas does not have a noticeable pathogenic rôle.

In 1917, Levy and Tronquet<sup>34</sup> stated that it does not seem proved that exposure to gas predisposes to tuberculosis.

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26 Elliott, J. H. Discussion, Tr Nat Tuberc A, Thirteenth Annual Meeting, 1917, p. 62.

27 Elliott, J. H. Pulmonary Conditions Simulating Tuberculosis, *Am Rev Tuberc* **2** 707 (Jan.) 1919.

28 Bernard, L. Discussion, *Bull et mem Soc med d hôp de Paris* **40**, 1074 (June 30) 1916.

29 Gimbert. Action des attaques de gaz sur la tuberculose pulmonaire. Réunion médicale de la Ve Armée, *Presse med*, Jan., 1917. Quoted by Sergeant, Simonin and Euthymiou.

30 Gimbert. Tuberculose et gaz asphyxiants, *Paris med*, Jan., 1918. Quoted by Sergeant, Simonin and Euthymiou.

31 Moricheau-Beauchamp. Les tuberculoses respiratoires et la guerre, *Progres med*, July 14, 1917. Quoted by Sergeant.

32 Leon-Kindberg, M., and Delherm, A. Sur le triage des tuberculeux aux armées, *Presse méd* **25** 645 (Nov 15) 1917.

33 Bernard, L., and Mantoux, C. Traumatismes de guerre et tuberculose pulmonaire, *Bull et mem Soc med d hôp de Paris* **41** 683 (May 18) 1917.

34 Levy, F., and Tronquet. Un cas d'intoxication par les gaz simulant la tuberculose pulmonaire, *Bull et mem Soc med d hôp de Paris* **41** 824 (June 29) 1917.

In 1918, Euthymiou <sup>35</sup> stated that if gases play a rôle in the development of tuberculosis, it seems that chlorine occupies the first rank. However, in 737 cases of tuberculosis, he found only nine patients who had been gassed.

In 1919, Achard <sup>36</sup> found only six cases of tuberculosis in 3,525 persons who had been gassed. He expressed the opinion that the condition was rare following gassing.

In the same year, Rist, Sergeant, Dopter and Clerc <sup>37</sup> spoke of the extreme rarity of tuberculosis following gassing.

In studying the condition of 441 persons who had been gassed with mustard gas, and whom they observed for a long period of time, Clerc, Ramond and Guilhaume <sup>38</sup> found only two cases of tuberculosis. One of these patients had shown loss of weight and hemoptysis before being gassed. They believe the condition to be extremely rare following gassing, and state that they have never seen the acute generalized form.

In 1919, Morris <sup>39</sup> stated that in examining old cases of persons who had been gassed, repeated examinations of the sputum failed to reveal tubercle bacilli.

In 1919, Meakins and Priestley <sup>40</sup> followed 700 consecutive cases of gas poisoning through all obtainable records. There was not one case of proved pulmonary tuberculosis in the series.

In 1919, Dennis <sup>41</sup> examined by roentgen ray the chests of a large number of gassed patients but did not find any cases of tuberculosis.

In 1919, Cowen <sup>42</sup> reported a study of "upwards of 150" cases showing the after-effects of gas poisoning, and stated that "the sputum of the great majority of patients was examined, often on several occasions, but in no instance were tubercle bacilli detected."

In 1919, Berghoff <sup>43</sup> served on the Camp Grant Board for the study of the after-effects of war gases on soldiers applying for pensions and gives the following as his conclusion with regard to tuberculosis:

35 Euthymiou, C. Étude sur la tuberculose pulmonaire post-traumatique, These de Lyon, 1918.

36 Achard, C. Les sequelles des intoxications par les gaz de combat, Bull Acad de med **81** 135 (Feb 4) 1919.

37 Rist, Sergeant, Dopter, Clerc. Discussion, Bull et mem Soc d hop de Paris, June 19, 1919. Quoted by Roubier.

38 Clerc, A., Raymond, L., and Guilhaume, H. Étude clinique des sequelles pulmonaires chez les yperites, Presse med **27** 477, 1919.

39 Morris, R. S. Clinical Observations on the Late Pulmonary Effects of Gassing. Contrib to Med & Biol Research, Dedicated to Sir William Osler **2** 1138, 1919.

40 Meakins, J. C., and Priestley, J. G. The After-Effects of Chlorine Gas Poisoning, Canad M A J **9** 968 (Nov) 1919.

41 Dennis, C. E. Pulmonary Fibrosis After Gassing, as Shown by X-Rays, M J Australia **2** 372 (Nov 1) 1919.

42 Cowen, S. O. The After-Effects of Gas-Poisoning, with Special Reference to the Lung Lesions, M J Australia **2** 369 (Nov 1) 1919.

43 Berghoff, R. S. The More Common Gases, Their Effect on the Respiratory Tract, Observation on Two Thousand Cases, Arch Int Med **24** 678 (Dec) 1919.

Gas victims, irrespective of the type of gas and severity of attack sustained, show no marked predisposition toward active pulmonary tuberculosis, or toward the reactivation of a healed or quiescent pulmonary lesion

In 1919, Miller <sup>44</sup> made the following statement

The infrequent development of pulmonary tuberculosis as the result of exposure to poisonous and irritating gases and of chest wounds raises the question as to whether we have not in the past overemphasized the dangers of mechanical irritation and trauma as exciting causes of active tuberculosis

In 1920, Mallic <sup>45</sup> stated that cases of tuberculosis referable to gassing were extremely rare

Benmussa <sup>46</sup> (1920), in analyzing the history of 300 cases of persons who had been gassed, found thirteen cases of pulmonary tuberculosis (4 per cent) These histories were selected from 20,000 histories in Sergeant's collection In discussing Benmussa's results in 1925, Sergeant <sup>47</sup> stated that the percentage exceeds those of the statistics of other authors, and that they seem to him the highest figures that one could admit

Of 162 persons who had been gassed and who showed respiratory sequelae Rousselot, <sup>47</sup> in 1920, found only one with tuberculosis He gives gas the lowest place as a factor predisposing to tuberculosis

In 1920, Sergeant and Haas <sup>48</sup> reported analyses of two groups of cases taken from Sergeant's 20,000 histories The first group of 245 histories of cases of persons who had been gassed, all of which showed respiratory sequelae, was chosen without reference to the clinical variety of the sequelae In these 245 cases, not a single case of pulmonary tuberculosis confirmed by tubercle bacilli in the sputum occurred

In the second group, they chose 1 600 "suspects" of tuberculosis In these 1,600 "suspects" they found eighty-five cases of persons who had been gassed Of these old cases, twenty had tuberculosis Sergeant <sup>47</sup> (1925), in discussing these results, points out that at first glance one is likely to conclude that tuberculosis is frequent in persons who have been gassed, that if one considers how these statistics arise, he is led to recognize that they emanate from a service of "suspects" of tuberculosis and not from a service of simple cases of persons who had been gassed, and that, in consequence, other factors giving rise to tuberculosis must intervene He further points out that this restric-

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44 Miller, J A Tuberculosis Among European Nations at War, *Am Rev Tuberc* 3 337 (Aug) 1919

45 Mallic, H Les sequelles pulmonaires de l'ypcrite, *J de med de Bordeaux* 91 9 (Jan 10) 1920

46 Benmussa, S Les sequelles pleuro-pulmonaires et mediastinales des intoxications par les gaz asphyxiants, *These de Paris*, 1920

47 Rousselot, H Les sequelles pulmonaires chez les intoxiques par gaz de combat, *These de Paris*, 1920

48 Sergeant, E, and Haas, J La tuberculose pulmonaire et les sequelles des intoxications par les gaz, *Médecine* 1 466 (May) 1920

tion is supported by the fact that the intoxication by the gas in these eighty-five cases was, in the majority of instances, benign and had not always necessitated evacuation

The conclusions of Sergeant and Haas,<sup>48</sup> after their extensive and careful studies, are that tuberculosis following as a direct cause of exposure to gas is exceptional

In studying 151 cases of persons who had tuberculosis Roubier,<sup>24</sup> in 1920, found that six of these had been gassed. He states, however, that he does not think that the gassing had much to do with the tuberculosis, and mentions the tendency of soldiers to exaggerate and to date all of their troubles from an exposure to gas, even though they got only a whiff of gas under their masks

Beauchant,<sup>49</sup> as medical consultant in the French army, had the opportunity to see numbers of cases of tuberculosis as well as large numbers of persons who had been gassed. He states that he does not believe that he has seen a single case in which the factor of gas could be looked on indisputably as the cause of tuberculosis, and that among all the persons observed by him who had been gassed with mustard gas and who presented pulmonary sequelae, tuberculosis was not present. Three of 1,206 persons who had tuberculosis had previously been gassed with chlorine

Among 300 persons who had been gassed, Hunt and Jones<sup>50</sup> found only two who showed signs of phthisis

In 1920, Simonin<sup>10</sup> published an exhaustive thesis on the relationship between gassing and pulmonary tuberculosis. He states that in fifty-three cases gathered from the literature, mustard was mentioned as the offending gas seven times, and the suffocants eighteen times. He concludes that the mean of all statistics shows that 1 per cent of persons who have been gassed become tuberculous, and that of the cases of tuberculosis in the military population, 2 per cent occur in persons who have been gassed previously. He considered that the latter statement is best established. He further concluded that gas is not so important in the etiology of tuberculosis as are factors of a general nature

In 1920, Wilson and Mackintosh<sup>51</sup> analyzed a series of 1,500 consecutive mustard gas casualties, and in speaking of Achard's work, they state

His view that phthisis is no more than a curiosity as a secondary complication after gassing is in agreement with our experience. We have seen but one example in our series, a case with hemoptysis three days after gassing, in whom at the end of a week tubercle bacilli were found in the sputum. This man had been perfectly fit till he was gassed. Achard points out that there

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49 Beauchant, quoted by Simonin (footnote 10)

50 Hunt, G. H., and Jones, quoted by Simonin (footnote 10)

51 Wilson, C. M., and Mackintosh, J. M. Mustard Gas Poisoning, *Quar J Med* **13** 201 (Jan) 1920

must be many with latent tubercle in the army, yet it is infinitely rare to find the disease light up after gassing. He brings forward experimental support of his conclusion that gas does not create in the lung a soil particularly favorable to the growth of the tubercle bacillus.

Hawes,<sup>52</sup> as regional consultant in diseases of the chest for the New England district of the United States Public Health Service, had a large experience with persons who had been gassed. He states that while gas may lead to the invasion of the bronchi by secondary organisms, yet in his experience tuberculosis plays a minor rôle in this secondary invasion.

Sandall,<sup>53</sup> a medical officer of the British Government, stated in 1922 that there had not been an instance of tuberculosis in the Oxford (England) area in the men pensioned because they had been gassed.

In 1922, Hankins and Klotz<sup>54</sup> selected 166 persons who gave a history of gassing, from 3,837 patients treated at the Johnson City (Tenn.) National Sanatorium. All of these patients had been confined in a hospital for a period of from twenty days to three months because they had been gassed. Sixty-six per cent of the 166 patients had a condition diagnosed as clinical tuberculosis, but the sputum was positive in only one case.

In 1922, Meade<sup>55</sup> summarized the histories of over 3,000 persons examined by the War Risk Insurance Bureau in Kansas City. As a result of his work, he made the following statement: "I now believe that we can say to the public upon the best authority (which is based upon universal observation) that a man is no more liable to tuberculosis as the result of gassing than is a man who has never been gassed."

The following paragraph may also be quoted from Meade:

I am convinced that all chemical irritants activate and produce certain pathologic changes in the lungs, but I do not believe that such irritants are responsible for tuberculosis and will call your attention to Major Gerald B. Webb's article upon the effects of the inhalation of cigaret smoke in tuberculosis. He concludes that tobacco inhalation is a protective agent against tuberculosis and cites his examination of recruits. There was a much greater number of nonsmokers discharged on account of tuberculosis than were of smokers, and there were fewer cases of tuberculosis among cigaret smokers than among pipe and cigar smokers, showing that the inhalation of the smoke caused an irritation which gave some degree of protection. It has been shown by clinicians for years that coal miners are less susceptible to tuberculosis than are those of ordinary occupations. The Italians observed that sulphur fumes retarded tuberculosis. In London before the trains were electrified the mephitic vapors in the underground tubes were supposed to be of value to the consumptive employees.

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52 Hawes, J. B. Diagnostic Pitfalls. The Late Effects of Gassing vs Tuberculosis, Boston M. & S. J. **185** 1 (July 7) 1921.

53 Sandall, T. E. The Late Effects of Gas Poisoning, Lancet **2** 857 (Oct 21) 1922.

54 Hankins, J. L., and Klotz, W. C. Permanent Pulmonary Effects of Gas in Warfare, Am. Rev. Tuberc. **6** 571 (Sept.) 1922.

55 Meade, R. H. The Late Effect of War Gas on the Lungs and Its Relation to Pulmonary Tuberculosis, J. Missouri M. A. **19** 385 (Sept.) 1922.

Francine later expressed analogous views, as will be seen in the following

As Consultant in Gas to the American Fourth Army Corps and resident physician-in-chief of the great gas hospital at Toul, France, Francine<sup>56</sup> had an enormous experience with soldiers who had been gassed. In 1922 he made the following statement

It is inconceivable that gas (as it is, and not what so many people consider it to be, or what it may have been) could reactivate tuberculosis, and available statistics and majority expert opinion go to prove that it does not do so. This view is endorsed by French, British and other authorities

Francine's testimony before the senate committee, as reported by Gilchrist<sup>57</sup> in 1924, paints such a vivid picture of his experience with soldiers who had been gassed, and expresses such decided opinions that it is deemed advisable to quote him rather extensively, as follows

During the war, of course, I saw very intimately the picture of gas in the field and in the hospital. And this having interested me from the professional point of view, I made a special point of studying the lungs of these gassed men, both clinically and at postmortem in the gas hospital. Clinically the acute picture of gassing, this mass inflammation, disguised the picture at times so that you could not clinically have diagnosed tuberculosis had it been present. But you could examine the sputum. Many of these men spat blood, and their sputum was uniformly negative.

While we were being rushed, and were too rushed to keep records, I suppose I can say that I saw then 100 to 125 posts. In a number of these cases it was perfectly and palpably evident to a man of pathological training that there were healed, nonactive lesions, which is not an uncommon occurrence, as you know. It is considered that probably 60 to 90 per cent of people have at one time or another had a tuberculosis infection. But these palpable latent lesions showed no evidence of activity, or reactivation, from four to six to ten weeks after the acute inflammation which is supposed to give rise to tuberculosis.

I was only in the hospital six or eight weeks, but there were a number of men unevacuatable on account of their condition, they had been severely gassed, and were recuperating, were feeble, were skin and bone, and so on, and they died from an intercurrent infection, which was rampant, as you know, influenza and bronchopneumonia, and they died, not in any sense due, except indirectly, to the gassing, but to this crossinfection. So that those men would have had plenty of time to develop signs of activity in those latent tuberculous lesions. For it takes anywhere from, we will say, two to three weeks for such evidence to appear macroscopically, grossly, for tubercles and localized inflammation to appear, indicating activity, and such would have developed by the time I saw them, if gas had had any effect, any effect whatever, in developing already existing tuberculosis or activity in a latent or healed state.

There was a similar group of cases who were orderlies. We were very short of nurses, and I did not discharge a certain group of men who had been gassed, but whom we had to keep in the hospital to help out as orderlies, these were

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<sup>56</sup> Francine, A. P. Tuberculosis and Poison Gas, *Tr. Nat. Tuberc. A.*, Eighteenth Annual Meeting, 1922, pp. 261-264, *New York M. J.* **117**: 25 (Jan. 23) 1923.

<sup>57</sup> Gilchrist, H. L. Warfare Gas and Tuberculosis, Testimony of Dr. Albert P. Francine Before the Senate Committee, *Mil. Surgeon* **54**: 470 (April) 1924.

quite a group. These men had been gassed, but were able to be about and help, carry trays, and so on. Some of these men died through infection, quite a number of them. And these men, again, showing milder pathological evidence of gas, having a history of gas, showed no sign of reactivation in latent lesions. And in the cases I examined postmortem, I should say there were at least twenty to twenty-five men who showed latent or healed lesions—that is perfectly plain latent lesions—and in not a single case was there any evidence of activity developed through gas.

I believe that so far from producing tuberculosis—anybody might, indeed, think so on account of the local irritation in the lungs and bronchi—gas may tend to prevent tuberculosis, and I will tell you why. Because its primary action is to produce congestion of the lungs. In fatal cases it causes severe inflammation followed by congestion and edema and prevents the aeration of the blood and quickly smothers, so to speak, the patient. He cannot get air into his lungs or blood. When the man drowns or smothers, he is suffering primarily from that inflammation caused not by a germ but a chemical. We know that a nonbacterial congestion or hyperemia is a favorable factor in tuberculosis. In other words, if we could produce locally in the lungs a congestion, we could go far toward curing tuberculosis. People with heart disease (I speak of this simply to you gentlemen as laymen, to explain some of my reasons)—people with heart disease, that type of heart disease known as mitral stenosis, where there is an increase in the blood in the lungs, do not suffer from tuberculosis.

Further, it has been claimed clinically that men who had tuberculosis and have been gassed run a more favorable, slower, more indolent course, are better off over the same period of time, improve more, than the same type of cases having tuberculosis but who have not been gassed.

The permanent effect of gas is the result of this irritation, this congestion, and what follows all inflammations and congestions, if they last long enough, is, broadly speaking, the destruction of the finer cellular tissue in places and its replacement by fibroid tissue.

And to that extent these postinfluenzal and postgas lungs show, in the very bad cases, the remains of this thing and it is still being mistaken for tuberculosis very widely. But they clear up. You take a man that has been gassed and X-ray him when he has recovered from acute symptoms. A plate taken two years later shows, instead of these dark shadows, marked evidence of clearing up. And they do clear up. Their health and strength improve markedly, too.

It is an interesting thing that clinically, these gas cases which have tuberculosis do not develop, as a rule, tuberculosis of the throat. You might suppose that where the inflammation had affected the throat originally and very severely, as it may, they would develop as a complication tuberculosis of the throat. They do not. You follow 100 men with tuberculosis who have not been gassed and 100 men with tuberculosis who have been gassed, and the percentage of throat complications, tuberculous laryngitis and of other complications, in the ungassed cases, will, it has been claimed, be greater than in the gassed cases, suggesting, at least, that in some way it inhibits it.

In 1922, Gilchrist<sup>58</sup> compiled an exhaustive report for the Chemical Warfare Service on the relationship between tuberculosis and warfare gases, extracts from which were published in the *Military Surgeon* of the same year. His report quotes many authorities and contains many interesting tables and figures, among which the following are included

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<sup>58</sup> Gilchrist, H. L. Tuberculosis and Its Relation to Warfare Gases, *Mil Surgeon* 50 609 (June) 1922.

Instead of the war increasing the number of tubercular cases, it has lessened them, this being especially true in the different armies, as shown in the following table

*Tuberculosis in Armies*

France	Early months of the war	1 75
	Last two years of the war	63
Great Britain	Before the war, entire army	1 1
	First seventeen months of war, entire army	1 1
Belgium	Before the war, entire army	35
	During the war, entire army	26
United States	Regular Army, 1917 to 1918	75
	National Army, during the war	67

Gilchrist<sup>59</sup> also quotes the following from the report of the Surgeon General of the Army for 1920

One hundred and seventy-three cases of tuberculosis occurred during 1918 and 1919 among the 70,552 men who had been gassed in action. Of this number, 78 had been gassed by gas, kind not specified, 8 by chlorine, 65 by mustard, and 22 by phosgene. The number of cases of tuberculosis for each 1,000 men gassed was 2.45. Since the annual rate of occurrence for tuberculosis among enlisted men serving in Europe in 1918 was 3.50, and in 1919, 4.30 per 1,000, it would seem to be apparent that tuberculosis did not occur any more frequently among the soldiers who had been gassed than among those who had not been.

Furthermore, Gilchrist quotes letters from numerous medical officers who had experience with soldiers who had been gassed during and after the war, and their verdict is almost unanimous to the effect that there is little, if any, relationship between tuberculosis and gassing.

In 1923, Brelet,<sup>60</sup> after studying large numbers of cases of persons who had been gassed, concluded that these men rarely become tuberculous.

McNaught,<sup>61</sup> in discussing the subject in the same year, expresses the same opinion, and says that Meakins and Walker<sup>62</sup> found only one case of tuberculosis in 163 persons suffering from long continued sequelae of being gassed.

Cole,<sup>63</sup> after four years' experience in Veterans' Bureau work, tuberculosis sanatoriums and private practice with soldiers who had been gassed, concludes

<sup>59</sup> Gilchrist, H. L. Report on the After Effects of Warfare Gases, Chemical Warfare Service, U. S. A., 1922.

<sup>60</sup> Brelet. Note sur les sequelles pulmonaires de l'intoxication par les gaz, Bull. et mem. Soc. med. d. hop. de Paris **47** 1458 (Nov. 2) 1923.

<sup>61</sup> McNaught, P. R. The Effects, Immediate and Remote, of Irritant Gas (Dichlorethylsulphide) Poisoning on Respiratory Tract, Tubercle **4** 345 (May) 1923.

<sup>62</sup> Meakins, J. C., and Walker, T. W. The After-Effects of Irritant Gas Poisoning, 1918. Quoted by McNaught.

<sup>63</sup> Cole, H. H. A Clinical Study of the Gassed Ex-Soldier with Special Reference to Pulmonary Tuberculosis, Am. Rev. Tuberc. **7** 230 (June) 1923.

War gassing has little to do with the development of later pulmonary tuberculosis. The gassed patient who later develops tuberculosis usually runs a less severe course with less tendency to serious complications than the non-gassed individual.

In 1924, Stewart<sup>64</sup> stated that tubercle bacilli are strikingly absent from the sputum of persons who had been gassed and who show respiratory sequelae. In over 100 cases studied, he found the sputum positive only three times.

In 1924, Spehl<sup>65</sup> stated that the action of gas does not favor the development of pulmonary tuberculosis. Pulmonary tuberculosis, he says, may develop in a patient who has been gassed, but it is difficult to impute it to the direct action of the gas.

Spehl and Dautrebande<sup>66</sup> did not find any instances of tuberculosis in seventy-six persons who had been gassed and who were observed by them. They express the opinion that tuberculosis is a rare sequel of gas, and state that no one has been able to demonstrate convincingly that gas causes the development of tuberculosis or the reactivation of an old lesion.

In his exhaustive article dealing with the late sequelae of gassing, published in 1925, Sergeant<sup>67</sup> states that one must conclude from a study of all the statistics that the pathogenic rôle of the war gases can be considered almost negligible. He then attempts to interpret the mode of action of the gas when tuberculosis follows intoxication with gas. There are two eventualities. Tuberculosis may immediately follow the intoxication, or it may appear later. In the few isolated instances in which tuberculosis has been reported in the acute or subacute form immediately following gassing, Sergeant thinks that the condition arises as the immediate result of two factors, which may be associated with each other or remain isolated: (1) the resowing of the bronchial tree by bacilli coming from lesions, active, but latent, which is favored by the alterations of the mucosa, (2) the profound taint of the organism due to the intoxication, and favored by other conditions (cold, jaded physique and other factors). As to the tuberculosis which occurs late following gassing, Sergeant comments that if one takes into consideration, first, the exceptional rarity of cases of tuberculosis following the action of gas, and, second, the great frequency of cases of intoxication by gas, one is led to conclude that the direct action of the gas can be considered negligible, and, further, to believe that indirect factors (diverse miseries

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64 Stewart, A. The Remote Results of "Gassing," *M. J. Australia* **2** 554 (Nov. 22) 1924.

65 Spehl, P. Les sequelles des gaz de combat, *Arch. méd. belges* **77** 1 (Jan.) 1924.

66 Spehl and Dautrebande. Les sequelles des gaz de combat, *Arch. méd. belges* **77** 768 (Sept.) 1924.

endured during a long campaign, long captivity, poor hygiene, alcoholism enervating maladies and other conditions), occasionally awaken old tuberculous lesions that have been more or less latent

Sergent further concludes that whatever may be said of these interpretations, it is incontestable that six years or more after the last possible exposure to gas one encounters some tuberculosis among persons who have been gassed. He is convinced that the longer the time since the end of the war, the more numerous will become the cases of tuberculosis among persons who were gassed during the war. This will signify only that the passage of years will have multiplied the chances for the intervention of the occasional circumstances which favor the reactivation of tuberculosis. It will not be allowable to relate an intoxication by gas which occurred some years before with such a reactivated tuberculous process.

The foregoing is a brief account of all the clinical experience and clinical opinions on the subject that I could find in the literature. It is clear that there is considerable consolidation of opinion. In order to have the matter definitely settled, it is necessary only to verify clinical opinion by direct experimental evidence. As stated before, there has been little experimental work bearing directly on the subject. The experiments of Achard and Flandin<sup>67</sup> have a direct bearing, but before relating their experiments, I shall briefly review those of several others which bear indirectly on the subject.

In 1886, Celli and Guarneri<sup>13</sup> conducted a series of experiments on dogs and rabbits to determine whether the inhalation of certain substances would lower the resistance of the animals to subsequent inhalations of dried tuberculous sputum. They first caused seven animals to inhale dried sputum in a special apparatus and found that only one of the seven developed tuberculosis. These were their controls. They then subjected four animals to inhalations of chlorine and subsequently caused them to inhale dried tuberculous sputum. None of the four animals developed tuberculosis. Two animals were then given an intratracheal injection of ammonia followed by inhalations of sputum. These experiments were negative so far as pulmonary tuberculosis was concerned. Scraping of the trachea was done in three animals. One of these animals developed pulmonary tuberculosis as demonstrated by the finding of the bacillus in the lung. In the same manner, four animals were given inhalations of sulphur dioxide. Of these animals, three were infected with pulmonary tuberculosis, while one remained healthy.

While their experiments were negative so far as the chlorine, ammonia and scraping of the trachea were concerned, and positive in the case of the sulphur dioxide, they do not appear to have been of great value, as too few animals were used and as the experiments were not often enough repeated.

<sup>67</sup> Achard and Flandin. *Note clinique et thérapeutique sur l'intoxication par les gaz*, Ministère de la Guerre, 1918.

Corper,<sup>68</sup> in 1919, found that certain local irritants—turpentine, cotton oil, tincture of cantharidin and tincture of capsicum—did not have an appreciable effect on the progress of tuberculosis in the guinea-pig, while lamp black had a distinctly retarding influence, and, finally, pulverized glass a markedly accelerating influence when injected with the bacilli. This is in keeping with the known clinical fact that phthisis is not so common among coal miners as among the ordinary population, in spite of the marked amount of anthracosis developed in the lungs from inhaled dust. On the other hand, workers in flint and quartz are especially liable to pulmonary tuberculosis.

The observations of Corper and Rensch,<sup>69</sup> in 1921, on the difference between the reaction of the tubercle bacillus and that of other pathogenic bacteria to leukotoxic agents are interesting and worth while quoting.

It is interesting in this connection that tuberculosis in the animal is not perceptibly influenced by agents and procedures having a profound effect on acute experimental infections. Corper and Chovey found that mice subjected to a single nonlethal exposure to the roentgen ray, capable however of producing a leukopenia, or given a nonfatal injection of thorium X, also capable of causing leukopenia, and shortly thereafter inoculated with pneumococci or hemolytic streptococci, human and bovine, revealed an increased susceptibility to all of these organisms, as indicated by an increased and earlier mortality among the treated animals and the earlier appearance in, and longer persistence of, the cocci in the blood as compared with animals subjected only to inoculation. Winteritz and his co-workers found that benzene had a similar effect on pneumococcus infection in rabbits, while Lawen found that prolonged roentgen-ray exposure of rabbits increased their susceptibility to staphylococcus infections, and that the resistance of mice to pyocyaneus and anthrax, and rats to anthrax was reduced by roentgenization. The tubercle bacillus, however, stands out distinctly from these organisms in respect to the leukotoxic agents as noted by Corper, Kellert, and Weinberg, the course of tuberculosis in guinea-pigs being uninfluenced by benzene, thorium X and the roentgen ray.

These authors also conducted a series of experiments to determine the action of mustard gas on the development of tuberculosis in guinea-pigs. They first found that mustard gas dissolved in 25 per cent glycerol is bactericidal toward virulent human tubercle bacilli after an exposure in vitro of at least one-half hour to 0.1 per cent, and after two hours to 0.01 per cent. They then found that mustard gas in 0.1 per cent strength in 25 per cent glycerol, containing virulent human tubercle bacilli, and injected immediately subcutaneously into guinea-pigs, entirely prevented the development of systemic tuberculosis, even 0.01 per cent mustard gas had a distinctly retarding influence on the development of

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<sup>68</sup> Corper, H. J. Further Attempts to Reduce the Resistance of the Guinea-Pig to Tuberculosis, The Effects of Various Local Irritants, *Am Rev Tuberc* **3** 605 (Dec.) 1919.

<sup>69</sup> Corper, H. J., and Rensch, O. B. The Effect of Mustard Gas (Dichloroethyl sulphide) on Experimental Tuberculosis, *J Infect Dis* **28** 286 (March) 1921.

tuberculosis in these animals. They also found that mustard gas given subcutaneously to guinea-pigs in amounts consistent with life (0.0001 cc in glycerol) in a single injection, or repeated at four day intervals for three or four injections, did not have an appreciable effect on the amount of anatomic tuberculosis resulting from the subcutaneous injections of virulent human tubercle bacilli.

In 1922, Conroy, Conroy and Laird<sup>70</sup> found that chlorine (6 parts per million) effectively rid the sewage from a sanatorium for tuberculosis of tubercle bacilli. Of twenty-four guinea-pigs inoculated with this effluent untreated with chlorine, twenty-one developed tuberculosis. None of the thirty inoculated with effluent after treatment with chlorine became tuberculous.

In 1918, Achard and Flandin<sup>67</sup> conducted a series of experiments to determine the direct effect of the inhalation of gas on the development of pulmonary tuberculosis. They submitted guinea-pigs to the repeated intoxications of carbon monoxide, and concluded that tuberculosis did not progress more rapidly and that it was not more severe in these animals than in control guinea-pigs inoculated the same day with the same dose of bacilli.

#### EXPERIMENTAL

While these last mentioned experiments are extremely interesting and of great value for their direct bearing on the relationship between gassing and the development of pulmonary tuberculosis, it seemed advisable to conduct further experiments, employing gases used in actual warfare, in the hope of more definitely settling the question of the relationship between tuberculosis in the ex-soldier and a history of gassing during the late war. To this end I have conducted experiments covering the past three and one-half years, in the course of which 335 rabbits were used. The gases used were mustard, phosgene and lewisite.

#### METHOD

The method employed in each set of experiments has been to use an equal number of controls and of animals inoculated with tubercle bacilli. The controls and inoculated animals have received the same amount of gas, both as to the time and concentration, in each instance. In order to simulate time relations between gassing and a possible infection with tubercle bacilli that might occur in actual warfare, I have inoculated different groups of animals at varying times before gassing, and other groups at varying times after gassing. In the former instances we hoped to simulate an old latent tuberculous lesion, and to

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70 Conroy, J. M., Conroy, B. B., and Laird, A. T. The Destruction of Tubercle Bacilli in Sewage by Chlorine, *Am. Rev. Tuberc.* 6: 63 (March) 1922.

determine whether gassing would have any effect on reactivating or accelerating the process. In the latter we attempted to determine the effect of gassing on the beginning of a new tuberculous infection.

Rabbits were used in all the experiments, as it is easier to produce pulmonary tuberculosis in them than in the other laboratory animals. All injections were made intravenously in the ear vein. This resulted in an active pulmonary tuberculosis, the extent of which could be controlled to a large degree by the size of the dose injected. The liver, kidneys and spleen were the other organs affected, but these were never affected to the same extent as the lungs. It was possible to produce a pulmonary tuberculosis without the involvement of other organs if the dose was kept small enough. Intratracheal injection was tried, but was not nearly so satisfactory as injection into the ear vein.

Glycerine broth cultures of virulent human tubercle bacilli were used in all the experiments. Young cultures were used in all instances. Varying doses were given, in milligrams per kilogram of body weight. In order to secure uniformity of weighing conditions, the fluid was poured off, and the culture was always allowed to drain for one-half hour before it was weighed. In the early experiments the large dose used produced tuberculosis in practically all animals inoculated. Later an effort was made to give doses so small that part of the animals that received injections would contract the disease and part would not. In this way, the effect of the gas as a phthisiogenic agent could be more easily determined.

In order to allow sufficient time for the development of tuberculous lesions, should there be any, animals were not killed in less than five weeks from the time of inoculation. This allowed plenty of time for the development of the lesion. Indeed, many animals died of tuberculosis in a much shorter period of time from the date of inoculation—several in three weeks, and one or two in two weeks.

An account was kept of the gain or loss in weight of all animals, but it proved valueless, and is not mentioned further in this paper. Rabbits are capricious in the matter of weight, some with well developed tuberculous lesions gain steadily, while others without tuberculosis or other demonstrable lesions lose weight with surprising rapidity.

All the animals gassed were gassed with as near the lethal dose of the gas employed as it was possible to give them without causing death. Even with this sublethal (i. e., below average lethal) dose some of the animals died from the effects of the gas. These large doses were used because we wanted to repeat as nearly as possible the conditions that prevailed for the soldiers that were the most severely gassed during the war.

Mustard and phosgene were selected as the principal gases for the experiments because they produce two distinct types of pulmonary lesions. Mustard produces an extensive necrotizing inflammatory reac-

tion involving the entire respiratory tract, including the lung parenchyma, phosgene produces an intense edema, so intense that in severe cases the patient actually drowns in his own body fluids. All the other war gases produce lesions which are gradations and combinations of these two extremes. Intercurrent infections, of course, are common to them all.

Examples of representative experiments are shown in the tables. In choosing the sets of experiments for these tables, an effort was made to make a variety of selections both as to the gas used and as to the length of time before and after the inoculation that the animals were gassed. The details of a rather large number of experiments are given

TABLE 1—Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

PHOSGENE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
45	5	5/15/24	Killed	36 days		++++	Liver spleen
46	5	5/15/24	Died	6 days			
47	5	5/15/24	Died	9 days			
48	5	5/15/24	Killed	36 days		++++	Liver, spleen, kidneys
49	5	5/15/24	Killed	36 days		++++	Liver
Gassed Animals							
50	5	5/15/24	Killed	36 days	20 hours after	++++	Liver spleen
51	5	5/15/25	Killed	36 days	20 hours after	++++	
52	5	5/15/24	Died	21 days	20 hours after	++++	
53	5	5/15/24	Killed	36 days	20 hours after	++++	Liver spleen
54	5	5/15/24	Died	4 days	20 hours after		

Eighteen day old glycerine broth culture used for inoculations  
The last five animals in the table were gassed with phosgene (concentration 0.29 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty hours after inoculation  
The plus marks indicate the number of lobes involved

in these tables. This is considered necessary for clarity. The results in the experiments not included in the tables were similar to the results in those included.

A casual glance at the tables clearly shows the verdict. Only a discriminating person would be able to say whether there was more or less tuberculosis in the animals that were gassed than in those that were not gassed. The amount of tuberculosis was uniformly the same in the controls and in the gassed animals throughout the experiments. This is true both as to the extent of the tuberculous lesions (number of lobes involved) and as to the severity of the lesions. The lungs, liver, spleen and kidneys of all animals were examined carefully, both grossly and microscopically, and the results given in the tables represent the sum total of the tuberculosis found by both methods of examination.

An exception to the conclusions of the preceding paragraph might be considered with respect to the cases in which lewisite was used, namely, if it could be said that any difference existed, there was less tuberculosis in the gassed animals than in the controls. This is clearly shown in

TABLE 2—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

PHOSGENE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
63	2.5	6/25/21	Killed	36 days		++++	
64	2.5	6/25/21	Killed	36 days		+	
65	2.5	6/25/21	Killed	36 days		++	
66	2.5	6/25/21	Killed	36 days		++++	
67	2.5	6/25/21	Killed	36 days		++	
Gassed Animals							
68	2.5	6/25/21	Died	14 days	20 hours after		
69	2.5	6/25/21	Killed	36 days	20 hours after		
70	2.5	6/25/21	Died	2 days	20 hours after		
71	2.5	6/25/21	Died	5 days	20 hours after		
72	2.5	6/25/21	Killed	36 days	20 hours after	++++	

Nine day old glycerine broth culture used for inoculations

The last five animals in the table were gassed with phosgene (concentration 0.54 mg. of phosgene in 1 liter of air for seven and one half minutes) twenty hours after inoculation

The plus marks indicate the number of lobes involved

TABLE 3—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

PHOSGENE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
78	2.5	7/11/24	Died	27 days		++++	Liver
79	2.5	7/11/24	Killed	16 days		+++	Spleen
80	2.5	7/11/24	Killed	16 days		++++	Liver
81	2.5	7/11/24	Killed	16 days		++++	Kidneys
82	2.5	7/14/24	Killed	16 days		++++	Liver
Gassed Animals							
73	2.5	7/11/24	Killed	16 days	20 hours after	++++	
74	2.5	7/11/24	Died	8 days	20 hours after		
75	2.5	7/11/24	Killed	16 days	20 hours after	++++	
76	2.5	7/11/24	Died	9 days	20 hours after		
77	2.5	7/11/24	Died	3 days	20 hours after		

Culture used was incubated for twenty two days then placed in the icebox for three days, and again incubated for three days before injection

The last five animals in the table were gassed with phosgene (concentration 0.49 mg. of phosgene in 1 liter of air for seven and one half minutes) twenty hours after inoculation

The plus marks indicate the number of lobes involved

tables 12 to 15. One of the experiments with phosgene (table 2) also shows less tuberculosis in the gassed animals than in the controls. This is in keeping with Francine's statement (given in this article) that gasping lessens the chances for the development of pulmonary tuberculosis, owing to the state of congestion produced in the lungs.

It is possible that other experiments with phosgene and mustard would have shown the same thing if smaller doses had been used for the inoculations. For convenience, in the tables the number of lobes involved has been used as the index of infection. In most of the phosgene and mustard experiments such large doses were used that all lobes, both of

TABLE 4—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

PHOSGENE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
194	5	3/7/25	Killed	77 days		++++	Kidney
195	5	3/7/25	Died	72 days		++++	
196	5	3/7/25	Died	25 days		++++	
197	5	3/7/25	Killed	77 days		++++	
198	5	3/7/25	Killed	77 days		++++	Kidney
199	5	3/7/25	Died	34 days		++++	
200	5	3/7/25	Killed	77 days		++++	Kidney
Gassed Animals							
201	5	3/7/25	Killed	77 days	37 days after	++++	
202	5	3/7/25	Killed	77 days	37 days after	++++	
203	5	3/7/25	Died	43 days	37 days after	++++	
204	5	3/7/25	Killed	77 days	37 days after	++++	
205	5	3/7/25	Died	51 days	37 days after	++++	

Nine day old glycerine broth culture used for inoculations.  
The last five animals in the table were gassed with phosgene (concentration 0.54 mg. of phosgene in 1 liter of air for seven and one-half minutes) thirty seven days after inoculation.  
The plus marks indicate the number of lobes involved.

TABLE 5—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

PHOSGENE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
214	1	5/2/25	Died	3 days			
215	1	5/2/25	Killed	41 days		++++	Liver
Gassed Animals							
216	1	5/2/25	Killed	41 days	21 days before	++++	
217	1	5/2/25	Killed	41 days	21 days before	++++	

Eight day old glycerine broth culture used for inoculations.  
The last two animals in the table were gassed with phosgene (concentration 0.51 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty one days before inoculation.  
The plus marks indicate the number of lobes involved.

the animals that were gassed and of those that were not, became infected. In most instances, however, the infection was not severe in any lobe, and on both gross and microscopic examinations a difference in the amount of tuberculosis in the gassed animals and in the controls could not be detected.

TABLE 6—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

MUSTARD							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
85	2.5	7/21/24	Killed	46 days		++++	Liver, spleen
86	2.5	7/21/24	Killed	46 days		++++	
87	2.5	7/21/24	Killed	46 days		++++	
88	2.5	7/21/24	Died	6 days		+++	
89	2.5	7/21/24	Killed	46 days		+++	
Gassed Animals							
90	2.5	2/21/24	Killed	46 days	20 hours after	++++	Liver
91	2.5	7/21/24	Died	27 days	20 hours after	+++	
92	2.5	7/21/24	Killed	46 days	20 hours after	++++	
93	2.5	7/21/24	Killed	46 days	20 hours after	++++	
94	2.5	7/21/24	Killed	46 days	20 hours after	+++	
95*	2.5	7/21/24	Killed	46 days	26 days before	+++	

Thirteen day old glycerine broth culture used for inoculations

\* Rabbits numbers 90 to 94, inclusive, were gassed with mustard (concentration 0.0114 mg of mustard in 1 liter of air for one hour) twenty hours after inoculation. Rabbit no 95 had been gassed with phosgene (concentration 0.54 mg of phosgene in 1 liter of air for seven and one-half minutes) twenty six days previous to inoculation.

The plus marks indicate the number of lobes involved

TABLE 7—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

MUSTARD							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
116	1	9/27/24	Killed	39 days		++++	Liver, spleen, kidney
117	1	9/27/24	Killed	39 days		++++	
118	1	9/27/24	Killed	39 days		++++	
119	1	9/27/24	Killed	39 days		++++	
120	1	9/27/24	Killed	39 days		++++	
121	1	9/27/24	Killed	39 days		++++	
Gassed Animals							
110	1	9/27/24	Killed	39 days	48 hours after	++++	Liver, spleen, kidney
111	1	9/27/24	Killed	39 days	48 hours after	++++	
112	1	9/27/24	Killed	39 days	48 hours after	++++	
113	1	9/27/24	Killed	39 days	48 hours after	++++	
114	1	9/27/24	Killed	39 days	48 hours after	++++	
115	1	9/27/24	Killed	39 days	48 hours after	++++	

A two to three weeks old glycerine broth culture used for inoculations

The last five animals in the table were gassed with mustard (concentration 0.0148 mg of mustard in 1 liter of air for one hour) forty eight hours after inoculation

The plus marks indicate the number of lobes involved

TABLE 8—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

MUSTARD							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
188	5	2/28/25	Killed	73 days		++++	
189	5	2/28/25	Killed	73 days		++++	
190	5	2/28/25	Killed	73 days		++++	
191	5	2/28/25	Killed	73 days		++++	
192	5	2/28/25	Killed	73 days		++++	
193	5	2/28/25	Killed	73 days		++++	
Gassed Animals							
182	5	2/28/25	Died	36 days	5 weeks after	++++	
183	5	2/28/25	Died	42 days	5 weeks after	++++	
184	5	2/28/25	Died	61 days	5 weeks after	++++	
185	5	2/28/25	Killed	73 days	5 weeks after	++++	
186	5	2/28/25	Killed	73 days	5 weeks after	++++	
187	5	2/28/25	Killed	73 days	5 weeks after	++++	Liver, spleen

Seven day old glycerine broth culture used for inoculations

The last six animals in the table were gassed with mustard (concentration 0.0138 mg of mustard in 1 liter of air for one hour) five weeks after inoculation

The plus marks indicate the number of lobes involved

TABLE 9—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

MUSTARD							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
122	1	10/4/24	Died	21 days		++++	Liver, spleen
123	1	10/4/24	Killed	34 days		++++	Liver, spleen, kidney
124	1	10/4/24	Died	16 days		++++	
125	1	10/4/24	Killed	34 days		++++	
126	1	10/4/24	Killed	34 days		++++	Liver, spleen, kidney
127	1	10/4/24	Killed	34 days		++++	
Gassed Animals							
128	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
129	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
130	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
131	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
132	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
133	1	10/4/24	Died	18 days	28 hours before	++++	Liver, spleen, kidney

Fourteen day old glycerine broth culture used for inoculations

The last six animals in the table were gassed with mustard (concentration 0.0145 mg of mustard in 1 liter of air for one hour) twenty eight hours previous to inoculation

The plus marks indicate the number of lobes involved

TABLE 10—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

MUSTARD							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
152	5	12/13/24	Killed	42 days		++++	Liver, spleen
153	5	12/13/24	Killed	42 days		++++	Spleen
154	5	12/13/24	Killed	42 days		++++	Liver
155	5	12/13/24	Killed	42 days		++++	Liver
156	5	12/13/24	Killed	42 days		++++	Spleen
157	5	12/13/24	Killed	42 days		++++	
Gassed Animals							
146	5	12/13/24	Killed	42 days	31 days before	++++	Liver, spleen
147	5	12/13/24	Killed	42 days	31 days before	++++	
148	5	12/13/24	Killed	42 days	31 days before	++++	Spleen
149	5	12/13/24	Killed	42 days	31 days before	++++	Liver
150	5	12/13/24	Killed	42 days	31 days before	++++	Liver, kidney
151	5	12/13/24	Killed	42 days	31 days before	++++	Liver, spleen

Fifteen day old glycerine broth culture used for inoculations

The last six animals in the tables were gassed with mustard (concentration 0.016 mg of mustard in 1 liter of air for one hour) thirty one days previous to inoculation. At the same time six other rabbits, not used in the experiment, were gassed with the same concentration, but died from the effects of the gas. This is mentioned only to indicate that the concentrations used were as near the lethal point as could be attained without killing all the animals.

The plus marks indicate the number of lobes involved

TABLE 11—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

MUSTARD							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
274	01	9/14/25	Killed	8 months		++++	Kidneys
275	01	9/14/25	Killed	8 months		++	
276	01	9/11/25	Killed	8 months		++	
277	01	9/14/25	Killed	43 days		++++	
278	01	9/11/25	Killed	43 days		+++	
279	01	9/14/25	Killed	43 days		++++	
Gassed Animals							
268	01	9/14/25	Killed	43 days	1 day after	++++	
269	01	9/14/25	Killed	43 days	1 day after	++++	
270	01	9/11/25	Died	10 days	1 day after		
271	01	9/14/25	Killed	8 months	1 day after	+	
272	01	9/11/25	Killed	8 months	1 day after	++	
273	01	9/11/25	Killed	8 months	1 day after	++	

Ten day old glycerine broth culture used for inoculations

The last six animals in the table were gassed with mustard (concentration 0.011 mg of mustard in 1 liter of air for one hour) twenty four hours after inoculation

The plus marks indicate the number of lobes involved

Animals inoculated with tubercle bacilli some weeks before gassing showed about the same amount of tuberculosis when they were killed several weeks after gassing as control animals that were inoculated at the same time with the same dose of bacilli. This tends to bear out the clinical observations that gassing does not reactivate an old tuberculous lesion.

Likewise, animals gassed at varying periods of time before inoculation with tubercle bacilli developed no more tuberculosis than did control

TABLE 12—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

LEWISITE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involve- ment	Other Organs Involved
Controls							
280	0.01	9/26/25	Killed	70 days		++++	
281	0.01	9/26/25	Killed	70 days		++	
282	0.01	9/26/25	Killed	70 days		++++	
283	0.01	9/26/25	Killed	70 days		+++	
284	0.01	9/26/25	Killed	70 days		++++	
Gassed Animals							
285	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	++++	
286	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	+	
287	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	+++	
288	0.01	9/26/25	Died	4 days	8 days before		
289	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	+++	
290	0.01	9/26/25	Died	26 days	8 days before and 6 days after		
291	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	++	

Four day old glycerine broth culture used for inoculations

The last six animals were gassed with the lewisite in a field test eight days before inoculation, and were gassed with the same gas in a gassing chamber (concentration 0.0069 mg. of lewisite in 1 liter of air for one hour) six days after inoculation.

The plus marks indicate the number of lobes involved.

animals inoculated at the same time with the same dose of bacilli. This again supports the view of those clinicians who believe that gassing does not have any influence on the development of new tuberculous lesions.

The results with animals gassed almost immediately (less than twenty-four hours) before or after inoculation with tubercle bacilli were the same as with those gassed for longer periods of time before or after inoculation.

TABLE 13—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

LEWISITE						
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement Other Organs Involved
Controls						
292	0.01	10/3/25	Died	22 days		++++ Spleen
293	0.01	10/3/25	Killed	67 days		++++
294	0.01	10/3/25	Killed	67 days		++++
295	0.01	10/3/25	Killed	67 days		++++
296	0.01	10/3/25	Killed	67 days		++++
Gassed Animals						
297	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	++
298	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	+ Kidney
299	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	+++
300	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	++++
301	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	+++

Eleven day old glycerine broth culture used for inoculations

All rabbits were gassed with lewisite in a field test fifteen days before inoculation. The last five animals in the table were also given the same gas in a gassing chamber (concentration 0.0073 mg. of lewisite in 1 liter of air for one hour) two days after inoculation.

The plus marks indicate the number of lobes involved.

TABLE 14—Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

LEWISITE						
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement Other Organs Involved
Controls						
318	0.05	12/19/25	Died	1 day		
319	0.05	12/19/25	Died	28 days		
320	0.05	12/19/25	Killed	42 days		++++
321	0.05	12/19/25	Missing			Missing
322	0.05	12/19/25	Killed	42 days		+++
323	0.05	12/19/25	Killed	42 days		++++
Gassed Animals						
312	0.05	12/19/25	Killed	42 days	5 days after	+ Kidney spleen
313	0.05	12/19/25	Killed	42 days	5 days after	+++
314	0.05	12/19/25	Killed	42 days	5 days after	++
315	0.05	12/19/25	Killed	42 days	5 days after	++
316	0.05	12/19/25	Killed	42 days	5 days after	++
317	0.05	12/19/25	Killed	42 days	5 days after	+++

Nine day old glycerine broth culture used for inoculations. The culture was not growing especially well.

The last six animals were gassed with lewisite (concentration 0.0067 mg. of lewisite in 1 liter of air for one hour) five days after inoculation.

The plus marks indicate the number of lobes involved.

The experiment tabulated in table 11 is interesting in that half of the gassed animals and half of the controls were kept for a much longer period of time than usual—eight months—before they were killed. The other half of both controls and gassed animals were killed at the end of six weeks, and all showed well developed tubercles in all lobes. It is reasonable to assume that at the time the first half were killed (six weeks after inoculation) the other half had about the same amount of tuberculosis. Keeping this latter half for a long period of time should then show the ultimate tendency of the existing tuberculosis. When these

TABLE 15—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

LEWISITE							
No	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
Controls							
330	005	2/6/26	Killed	42 days		+	
331	005	2/6/26	Killed	42 days		+	
332	005	2/6/26	Killed	42 days		++++	
333	005	2/6/26	Killed	42 days			
334	005	2/6/26	Killed	42 days			
335	005	2/6/26	Died	14 days			
Gassed Animals							
324	005	2/6/26	Killed	42 days	1 day before	++++	
325	005	2/6/26	Killed	42 days	1 day before	+	
326	005	2/6/26	Killed	42 days	1 day before	+	Spleen
327	005	2/6/26	Killed	42 days	1 day before		
328	005	2/6/26	Killed	42 days	1 day before	+	
329	005	2/6/26	Killed	42 days	1 day before		

Ten day old glycerine broth culture, growing luxuriously, used for inoculations.  
 The last six animals were gassed with lewisite (concentration 0.006233 mg of lewisite in 1 liter of air for one hour) twenty four hours previous to inoculation.  
 The plus marks indicate the number of lobes involved.

TABLE 16—*Incidence of Lesions in Spleen, Liver and Kidneys*

	Total Number	Spleen	Liver	Kidneys
Gassed animals	115	26	32	16
Controls	117	19	38	13

animals were killed at the end of the eight months' period, the number of active tubercles was much less than that in the first group killed, and a number of tubercles were in the process of healing.

The incidence of tuberculous lesions in organs other than the lungs is shown in table 16. Only those animals are included in the total number of gassed animals and controls that lived long enough after inoculation to have an opportunity to develop tuberculosis. A number of both gassed animals and controls died within a few days after gassing or after inoculation—some from the effects of the gas, others from other causes. These are not included in the total figures, as they have no bearing on

the case, and would only obscure the issue. It would be difficult to tell from the table which were in better condition—the spleen, liver and kidneys of the gassed animals, or those of the controls. There was slightly more tuberculosis of the spleen and kidneys in the gassed animals, while the liver was invaded more often in those that were not gassed.

Table 17 shows the incidence of lung involvement in the animals that were gassed and in those that were not gassed. It was exactly the same in the two sets of animals. However, when the total number of lobes involved were studied it was seen that the tuberculosis was more extensive in the controls than in the gassed animals.

Several interesting chance observations were made while studying the many microscopic sections from the animals used in these experiments. These are shown in figures 1 to 8. They represent various stages in an invasion of vessel walls by tubercle, and are interesting in relation to the development of acute milary tuberculosis. Figures 1

TABLE 17—*Incidence of Lesions in the Lungs and in the Lobes of the Lung*

	Total Number	Total Number with Lung Involvement	Total Number of Lobes Involved
Gassed animals	115	112	392
Controls	117	113	421

and 2 show small veins almost completely surrounded by tubercles. Figure 3 shows tuberculous involvement of an arterial wall, while figures 4 to 8 show tubercles which have broken through the walls of arteries and veins and have projected themselves into the lumen of the vessel. In one of the latter the tubercle is still covered by the intima of the vessel, while in the others the intima also has been broken through, and the tuberculous mass is washed constantly by the passing stream of blood.

That lesions of this type are not rare is well indicated by the textbooks of pathology. Adam and Nicholls,<sup>71</sup> in discussing milary tuberculosis, state "The condition often arises from the discharge of a caseating lymph-gland into a vein or from tuberculosis in the neighborhood of the receptaculum chyli and thoracic duct."

DeLafield, Prudden and Wood<sup>72</sup> make the following statement "A general infection may occur by the diffusion through the body of bacilli derived from a local tuberculosis, such as tuberculosis phlebitis or arteritis, or tuberculous inflammation of the thoracic duct."

<sup>71</sup> Adam, J. G., and Nicholls, A. G. Principles of Pathology, Philadelphia, Lea & Febiger, ed 2, 1911, p. 318.

<sup>72</sup> DeLafield, F., Prudden, T. M., and Wood, F. C. A Textbook of Pathology, New York, William Wood & Company, 1921, p. 282.

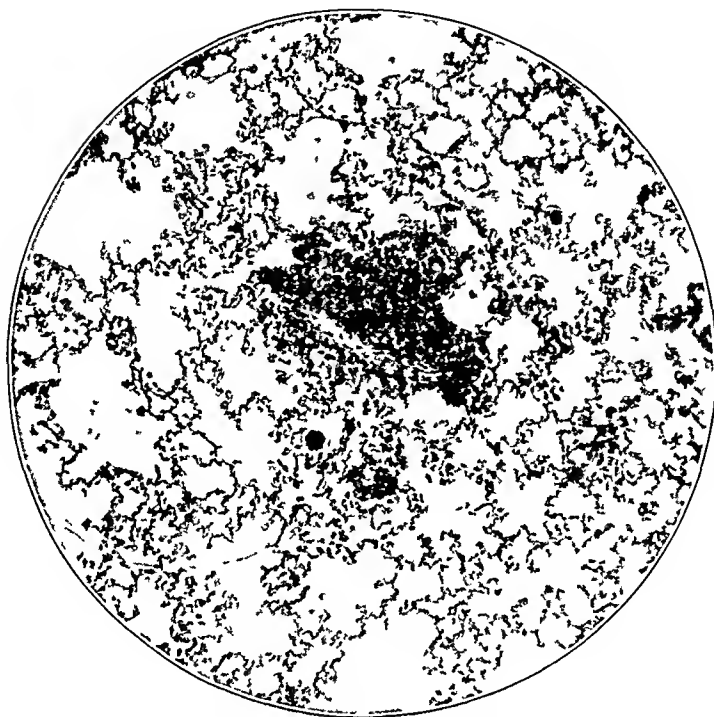


Fig 1—Tubercle partially surrounding a small vein Animal killed thirty-nine days after inoculation

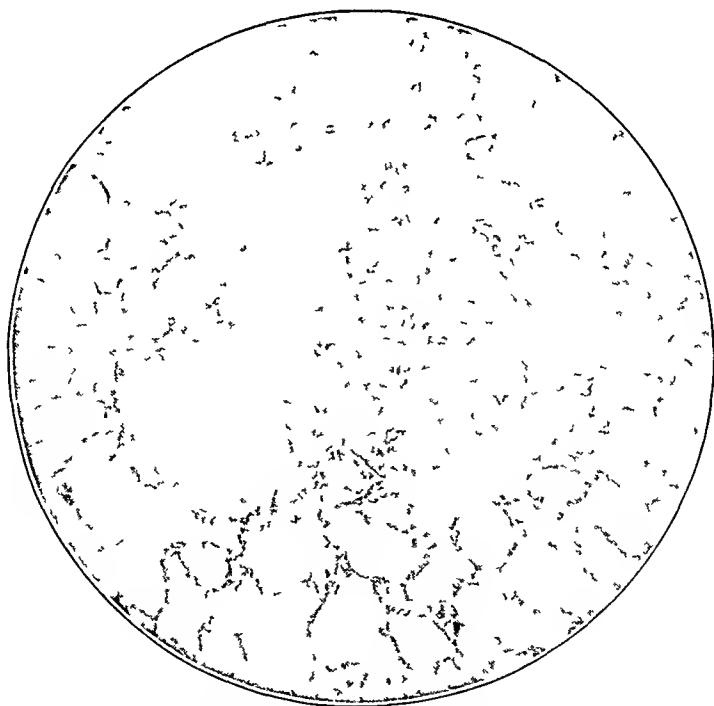


Fig 2—Small vein almost completely surrounded by tubercle Animal killed thirty-five days after inoculation

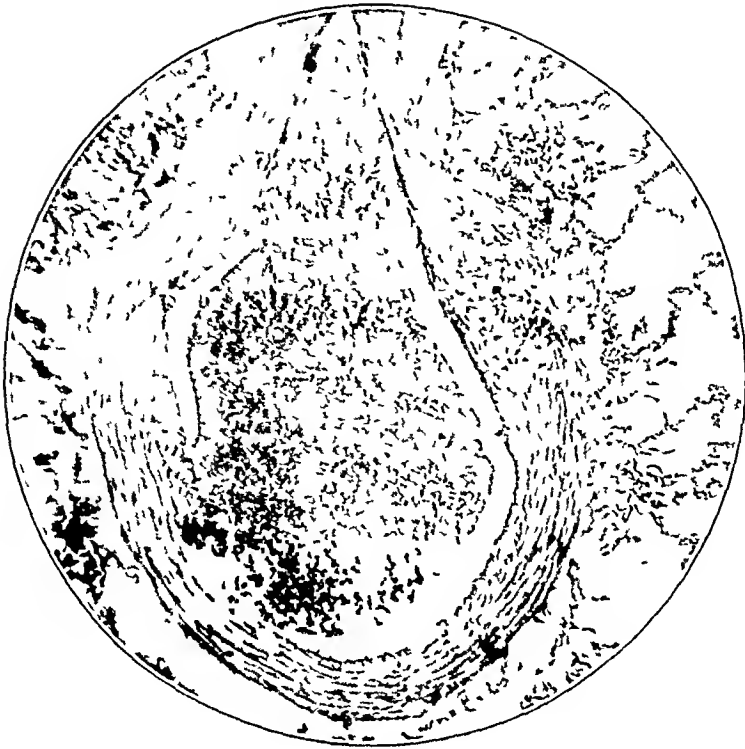


Fig 3—Tubercle of arterial wall Animal killed thirty-five days after inoculation

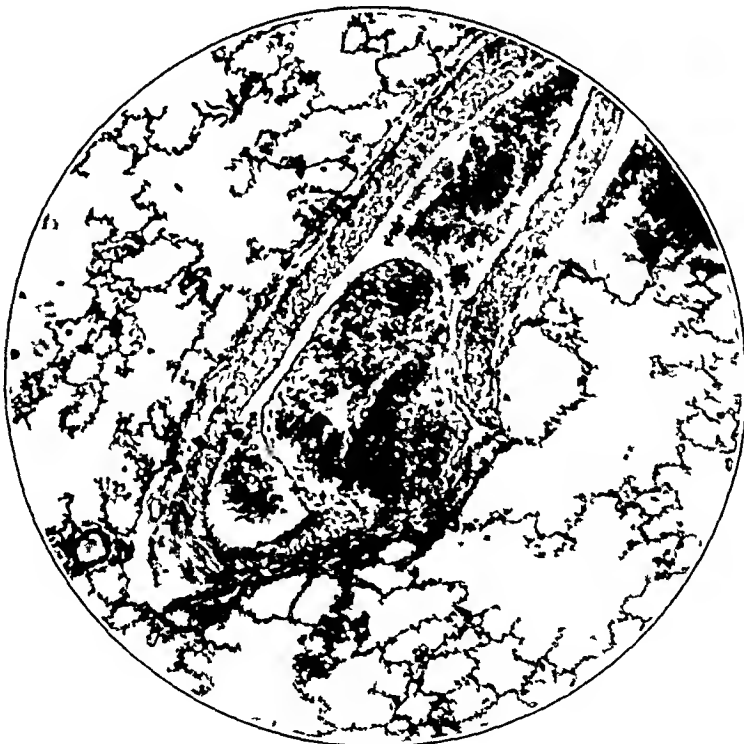


Fig 4—Tubercle projecting into the lumen of an artery Note that the tuberculous mass is still covered by intima Animal killed thirty-nine days after inoculation

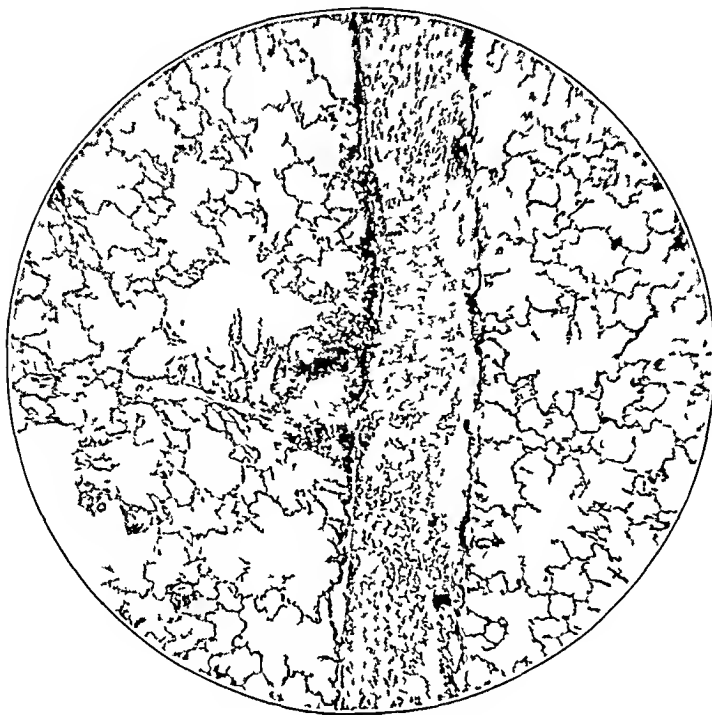


Fig 5—Tubercle projecting into lumen of a vein There is a complete break in the wall of the vein, intima included, so that the tuberculous mass can be freely washed by the blood stream Animal killed forty-two days after inoculation

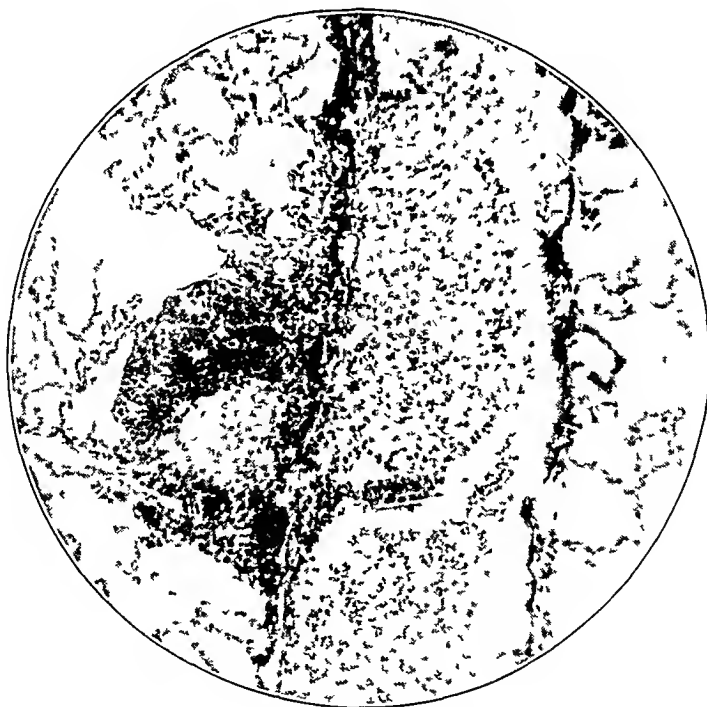


Fig 6—Higher power magnification of figure 5

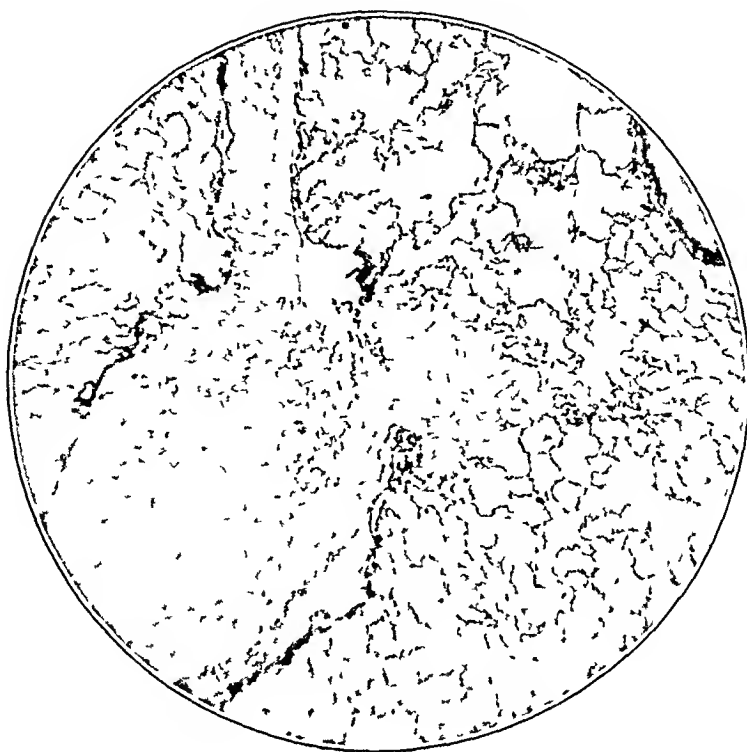


Fig 7—Tubercle projecting into the lumen of a vein Complete break in vein wall, including intima Animal killed forty-two days after inoculation

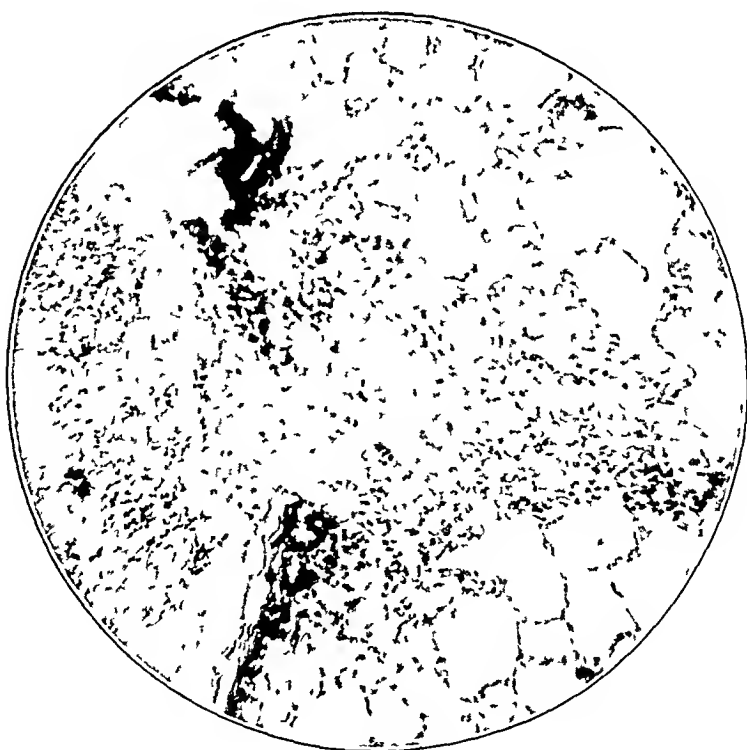


Fig 8—Higher power magnification of figure 7

MacCallum,<sup>73</sup> in speaking of the focus of dissemination of bacilli in acute miliary tuberculosis, says

It is perhaps most usual to find the portal of entry in a branch of the pulmonary vein, and it proves especially common to find that a caseous lymph-gland attached by adhesion to the vein-wall is the source of the material. When the vein is laid open in the right place, it is found to be partly obstructed by a granular, cheesy mass, projecting into its lumen in such a way that the soft, bacillus-laden material is washed by the passing stream into the general current, or else there is a hole in the wall opening into a cavity in an adherent caseous tissue from which the bacilli are swept by an eddy of the stream out into the vessel. The discharge of the bacilli in either case is soon limited by the deposit of a protective covering of thrombus material on the exposed surface.

He states further

The distributing tuberculous lesion may be found on the endothelial lining of the vessel (or even through the entrance of bacilli into the vasa vasorum), and set free new and abundant bacilli only when it has become caseous. This is especially true of the thoracic duct, which receives bacilli through its branches and comes in time to be lined with caseous, ulcerating areas from which newly grown bacilli are poured off into the blood. Rarely one may find tuberculous caseous lesions in the heart discharging bacilli into the blood. Intimal tubercles and erosions in the aorta and smaller arteries are uncommon, and distribute their bacilli into a limited area only.

Finally, in 1905, Silvergleit<sup>74</sup> was able by careful searching to find a vascular tubercle in 95 per cent of the cases of miliary tuberculosis studied by him. It was most frequently located in the pulmonary vein, but was occasionally found in the thoracic duct, aorta and other vessels.

In spite of the comparative frequency of lesions of this type, as exemplified by published accounts, they seemed to me to be uncommonly enough seen in the course of the day's work to justify my giving them a passing consideration in this article.

#### CONCLUSIONS

These experiments demonstrate clearly that rabbits gassed with phosgene, mustard and lewisite are not more susceptible to tuberculosis than are control animals inoculated at the same time with the same dose of bacilli. The gassing of animals that already have well developed tuberculosis does not appreciably accelerate the tuberculous process. The sum total of the amount of tuberculosis in all the experiments was slightly less in the gassed animals than in the controls.

73 MacCallum, W. G. *Textbook of Pathology*, Philadelphia, W. B. Saunders Company, ed. 2, 1921, p. 654.

74 Silvergleit, H. *Beiträge zur Entstehung der akuten allgemeinen Miliartuberculose*, *Virchows Arch.* **179** 283, 1905.

# PERIARTERITIS NODOSA

WITH SPECIAL REFERENCE TO THE ACUTE ABDOMINAL  
MANIFESTATIONS REPORT OF TWO CASES \*

HARRY A SINGER, M D

CHICAGO

The direct relationship between the knowledge of the manifestations of a certain disease and the frequency with which it is recognized is well exemplified by the morbid condition known as periarteritis nodosa. Between the time the disease was first described by Kussmaul and Maier <sup>1</sup> and the date of publication of Schreiber's review of the literature in 1904 a period of thirty-eight years, only fifteen additional cases had been recorded in medical archives. The authentic cases gathered by Ophuls in 1923 totaled seventy which number represents an additional fifty-three reported within a space of nineteen years. The recent summary by Gruber <sup>4</sup> of the cases found in the literature includes a description of 117 reports, to which may be added one by Frommel <sup>5</sup> four by Christeller <sup>6</sup> one by Paul <sup>7</sup> five by Arkin <sup>8</sup> and two by me bringing the total up to 130, an increase of sixty within three years. The increased number of case reports within the past few years points *a priori* to a more widespread and thorough knowledge of the character of the malady rather than to a more frequent occurrence of the disease.

Periarteritis nodosa has aroused greater interest and attracted more attention on the continent of Europe than elsewhere due in part to the fact that the disease was first described and studied in Germany, but more especially to the circumstance that a considerably larger number

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1 Kussmaul, A and Maier R. Ueber eine bisher nicht beschriebene eigenthumliche Arterienkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, Deutsches Arch f klin Med **1** 484, 1866

2 Schreiber, R. Ueber Polyarteritis nodosa, Inaug Diss., Konigsberg, 1904

3 Ophuls, W. Periarteritis Acuta Nodosa, Arch Int Med **32** 870 (Dec) 1923

4 Gruber, G B. Kasuistik und Kritik der Periarteritis nodosa. Zentralbl f Herz u Gefasskrank **18** 9-14, 1926

5 Frommel, E. L'arterite nodeuse, documents cliniques et anatomiques d'un cas nouveau, Ann de med **19** 42, 1926

6 Christeller, E. Ueber die Lokalisationen der Periarteritis nodosa besonders in den Bauchorganen, Arch f Verdauungskr **37** 249 1926

7 Paul. Vereinigung der pathologischen Anatomen Wiens, Sitzung vom 26 April, 1926, Wien klin Wchnschr **39** 1123, 1926

8 Arkin, A. Personal communication

of postmortem examinations are held there. The importance of the autopsy in the recognition of the disease is readily appreciated when one learns that only 7 per cent of the cases have been recognized *intra vitam* (Meitens<sup>9</sup>). Besides the German and Austrian writers, many Hungarian authors have contributed to the voluminous literature on the subject which appears in German. In our language six reports of authentic cases are found in medical publications of England (Dickson,<sup>10</sup> Muir and Bruce,<sup>11</sup> Beattie and Douglas,<sup>12</sup> Cameron and Ludlow,<sup>13</sup> Carling and Hicks<sup>14</sup> and Wordley<sup>15</sup>) and thirteen in medical journals of the United States, including the two cases to be reported in this article.

The first case of periarteritis nodosa to be reported in this country is one from Osler's medical service at Johns Hopkins Hospital by Sabin<sup>16</sup> in 1901. Although the symptoms were similar to those described in the cases previously reported, the two excised skin nodules instead of presenting evidence of periarteritic inflammation were composed entirely of lime salts. Since autopsy was not permitted and conclusive proof of the presence of the disease is lacking, this case is not included in the thirteen here referred to. The first established case of periarteritis nodosa in the United States was reported by Longcope<sup>17</sup> in 1908. His publication was followed in 1911 by the respective reports of Cooke<sup>18</sup> and Lewis,<sup>19</sup> describing cases observed also in Philadelphia. Lamb<sup>20</sup> reported two cases in 1914, and Klotz'<sup>21</sup> article concerning two additional cases appeared in 1917. The reports of

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9 Mertens, E. Ueber Periarteritis nodosa mit Massenblutung ins Nierenlager, *Klin Wchnschr* **1** 1841, 1922.

10 Dickson, W. E. Pathological Society of Great Britain and Ireland, Meeting of Jan 12, 1907, *Lancet* **172** 226, 1907.

11 Muir and Bruce. Pathological Society of Great Britain and Ireland, Meeting of Jan 12, 1907, *Lancet* **172** 226, 1907.

12 Beattie, J. M., and Douglas, M. A Case of Polyarteritis Acuta Nodosa, *J Path & Bact* **17** 195, 1912.

13 Cameron, H. C., and Ludlow, P. P. A Case of Periarteritis Nodosa, *Guy's Hosp Rep* **69** 159, 1918.

14 Carling, E. R., and Hicks, J. A. B. A Case of Periarteritis Nodosa, *Lancet* **204** 1001, 1923.

15 Wordley, E. A Case of Cortical Necrosis in the Kidney with Polyarteritis Acuta Nodosa, *Lancet* **205** 927, 1923.

16 Sabin, F. A Case of Arterial Disease Possibly Periarteritis Nodosa, *Bull Johns Hopkins Hosp* **12** 195, 1901.

17 Longcope, W. T. Periarteritis Nodosa, *Bull Ayer Clin Lab Penn Hosp, Philadelphia* **5** 1, 1908.

18 Cooke, J. V. A Case of Periarteritis Nodosa, *Proc Path Soc* **14** 96, 1911.

19 Lewis, P. A. Report of a Case of Periarteritis Nodosa, *Proc Path Soc* **14** 134, 1911.

20 Lamb, A. R. Periarteritis Nodosa—A Clinical and Pathological Review of the Disease with a Report of Two Cases, *Arch Int Med* **14** 481 (Oct) 1914.

21 Klotz, O. Periarteritis Nodosa, *J M Research* **37** 1, 1917-1918.

Ophuls,<sup>1</sup> Manges and Bachr,<sup>2</sup> Harris and Friedrichs<sup>3</sup> and of Keegan<sup>24</sup> followed in the order given

Due to the fact that more than nine tenths of the cases of periarteritis nodosa are not recognized until the time of autopsy and at times not until microscopic sections of the postmortem material are studied, most of the detailed reports in the literature are furnished by pathologists, with only a brief summary of the clinical data. As Sack<sup>25</sup> observes, the disease is disposed of in textbooks and systems of internal medicine in a few lines, whereas in treatises on pathologic anatomy lengthy and detailed descriptions are accorded the subject. On this account it is deemed advisable to stress the clinical side of the two cases reported in this article in spite of the fact that far more study was expended on the pathologic material. A second and perhaps more cogent reason for emphasizing the clinical aspect of periarteritis nodosa is that a better knowledge of its perplexing symptomatology will unquestionably lead to a more frequent and earlier recognition of the disease, which is essential to the elucidation of its etiology. At present the opportunity for the search of the causative agent at the most favorable time, that is, at the beginning of the disease is rarely afforded the clinician or the laboratory worker, since the underlying condition is first discovered, as a rule, at autopsy.

#### REPORT OF CASES

**CASE 1—History**—I S, a man, aged 29, was admitted to the medical service of the Cook County Hospital on Oct 7, 1923, complaining of epigastric pain, jaundice, epistaxis and melena. The onset, dating back five weeks, was insidious, with constipation, anorexia, occasional vomiting and epigastric distress. The abdominal discomfort was of a dull continuous type subject to acute exacerbations in the form of a cramplike pain. Two weeks before entrance, the patient noticed that his sclerae were jaundiced. At this time he experienced, in addition to dimness of vision, xanthopsia and headache. Three days prior to admission he was seized with severe epigastric cramps which led him to resort to an enema following the introduction of which large masses of clotted blood were passed. Noschleed occurred for two hours on the day of the hemorrhage from the bowel and recurred for a longer period the day preceding the patient's admission to the hospital.

In a general inventory of symptoms by systems, nocturia four to five times a night and urgency of urination were elicited. His past history indicated the occurrence of an attack two years previous similar to the present one except for the absence of jaundice. He admitted a Neisserian infection and a hard chancre fifteen and ten years ago, respectively.

**Physical Examination**—This disclosed a well developed colored man with marked jaundice of the sclerae and mucous membranes. The essential observa-

<sup>22</sup> Manges, M., and Bachr, G. Periarteritis Nodosa, *Am J M Sc* **162** 162, 1921.

<sup>23</sup> Harris, W. H., and Friedrichs, A. V. Periarteritis Nodosa with a Classification of the Pathology, *J M Research* **43** 285, 1922.

<sup>24</sup> Keegan, J. J. Primary Vascular Nephritis or Renal Periarteritis Nodosa, *Arch Int Med* **36** 189 (Aug) 1925.

<sup>25</sup> Sack, F. Zur Klinik der Periarteritis nodosa, *Med Klin* **20** 44, 1924.

tions consisted of an enlargement of the heart, mainly to the left, and a systolic murmur heard best over the apex and widely transmitted. The upper margin of the liver was found, on percussion, to be in the fourth interspace, the lower border, two fingerbreadths below the costal margin. Tenderness was elicited in the epigastrium. A generalized superficial adenopathy of slight degree was present. The blood pressure was 200 systolic and 140 diastolic.

*Laboratory Observations*—Urinalysis showed the presence of bile and albumin. The white blood count was 11,000, and 4 per cent of the cells were eosinophils. The red cell count was 2,260,000, and the coagulation time (watch crystal method) was three and one-half minutes. The stool apparently contained bile pigment, for it was light brown.

*Diagnosis*—Following the admission of the patient, the diagnosis rested between a catarrhal jaundice and a diffuse syphilitic hepatitis. In addition, a chronic nephritis with consequent hypertension and cardiac hypertrophy were assumed to be present.

*Subsequent Course*—The visible jaundice subsided somewhat, the stools became darker, and the urine showed less bile. Repeated attacks of epigastric pain associated with nausea and vomiting, however, kept the patient in an uncomfortable state.

On October 25, the following notation was made: "The patient has been having considerable localized epigastric pain of a severe cramplike nature and has vomited twice this morning. There is moderate tenderness and resistance in the right infracostal region. The acute cramplike pain suggests the presence of a biliary stone which is causing incomplete obstruction."

Repeated hemorrhage from the nose and bowel was a prominent feature throughout the course of the disease. The degree of jaundice varied. The epigastric pain, at times only slight, was practically continuous.

The notation recorded on October 30, reads: "The course of the illness points to a duodenal ulcer associated with cholecystitis and local peritonitis. The possibility of a perforation of the gallbladder into the stomach or duodenum should be considered. The hypertension of 200 mm. in an individual 29 years of age is due most likely to an underlying nephritis to which the ulcer, if present, might be related, the absence of retention of nonprotein nitrogenous substances would render a nephritic origin of a gastric or duodenal ulcer unlikely." The patient was placed on the Sippy treatment for ulcer, but failed to respond to the antacid therapy.

Pain was the most outstanding feature of the clinical picture, although it varied greatly in degree. After a sleepless night due to epigastric cramps, on November 6 the patient had an attack of such excruciating pain as to cause him to cry out. Surgical intervention was deemed advisable, and the patient was transferred to the surgical service.

The laboratory observations, in addition to those recorded at the time of entrance, included two negative blood Wassermann tests, gastro-intestinal roentgen-ray examination which failed to demonstrate the presence of any lesion, an Ewald test meal with an acidity of 68 free and 92 total and a positive test for chemical blood. No food particles or raisins were recovered six hours after the ingestion of a motor meal. The daily urinary output varied between 740 and 2,500, averaging about 1,300 cc. The specific gravity of the urine was fixed, being recorded constantly as 1.008 or 1.010. Albumin and casts were reported in most specimens. Chemical examinations of the blood (three) failed to show a consistent degree of retention. Successive blood counts showed the presence of a high grade secondary anemia, the red count ranging between 1,245,000 and 1,870,000. A single blood culture yielded staphylococci which were assumed to be contaminating organisms. The temperature throughout the course was subfebrile, usually between normal and 99.6 F. The pulse rate averaged from 80 to 90 beats per minute and the respiratory rate was, as a rule, between 24 and 26.

*Surgical Service Date*—The day following his arrival in the surgical ward (Nov 7, 1923), the patient developed hematemesis, an occurrence which further complicated the picture. The preoperative summary made by the surgeon reads: "In view of the history of attacks of pain simulating gallbladder colic, and findings of jaundice of an obstructive type, a palpable mass in the right upper quadrant, leukocytosis and a low grade temperature, rupture of an empyema of the gallbladder into the duodenum is suspected. The hemorrhages may be due to the cholemic state or to a hemorrhagic diathesis dependent on the underlying disease process. The prognosis in view of the presence of a high grade anemia is grave."

At the operation, performed on Nov 8, 1923, the gallbladder was bound by dense fibrous adhesions to the pyloric portion of the stomach and duodenum. When the fundus of the gallbladder was separated from the duodenum, a defect in the serosa of the latter was discovered but was not probed. Infiltration about this point was not felt. The gallbladder when in situ was considered to be filled with blood, as was also a limited portion of jejunum. There were multiple adhesions of the small intestines. The defect in the duodenum was repaired and the gallbladder extirpated. The diagnosis at operation was Henoch's purpura.

With the aid of hypodermoclysis and blood transfusion, the patient passed through a rather uneventful convalescence. On the thirteenth day after operation Nov 21, 1923, the patient left the hospital feeling greatly improved.

*Readmission to the Hospital*—The patient returned to the hospital on Feb 21, 1924, exactly three months after the date of his discharge, on this occasion he was admitted to another medical service. Subsequent to the time of his discharge, he was apparently improved according to his mother, but he was suffering from inconstant recurrent attacks of mild epigastric pain which only occasionally became sharp. The icterus, headache and constipation had been greatly relieved whereas evidences of hemorrhage had entirely disappeared. About a month following the operation, shortness of breath manifested itself, this increased gradually and was accompanied by a subcutaneous edema spreading from below upward. The semicomatose state in which the patient was seen at the time of entrance had been present since the previous day.

The physical observations were those of a myocardial insufficiency, the dependent edema being high grade. The urine, which had a specific gravity of 1.026, contained a moderate amount of albumin, many red and a few white cells and many hyaline and granular casts. The systolic blood pressure measured 152 mm, the diastolic, 130 mm.

The diagnosis of the presenting condition was given as broken compensation secondary to chronic diffuse nephritis. The patient died within twenty-four hours after entering the hospital; therefore this became a coroner's case. Autopsy was not performed by the coroner's physician.

*Summary of Clinical History*—A colored man, aged 29, was stricken with anorexia and constipation followed by colicky epigastric pain at times associated with vomiting. Deep jaundice and its concomitants followed, also repeated attacks of epistaxis and melena. The unrelated symptom of nocturia was traced to a chronic nephritis, as determined by laboratory methods. The blood pressure was 200 systolic and 140 diastolic. Severe attacks of pain in the upper part of the abdomen led to the diagnosis of cholecystitis, associated perhaps with a duodenal ulcer. The symptomatology referable to gallbladder disease dominated the picture to such a degree that in spite of the severe anemia developed as a result of the epistaxis, melena and hematemesis which rendered the patient a poor surgical risk, operative intervention was considered indicated. At the operation the jejunal content was seen to be hemorrhagic and a gallbladder distended by blood was removed. The patient died three months later with evidence of myocardial insufficiency secondary to a chronic nephritis.

*Pathologic Report*—Gross examination of the extirpated gallbladder submitted to the central laboratory revealed a recently removed gallbladder and a mass of clotted blood. The gallbladder, which had been opened, measured 9 cm in length and had a maximum circumference of 9.5 cm. The serous coat was roughened in places by fibrous tags, its color was pale pinkish red with dark blue circular spots scattered here and there over its surface. These dark spots corresponded in location to firm nodules measuring from 2 to 4 mm in diameter which were located within the wall of the gallbladder. When some of these nodules were sectioned, they were seen to consist of thrombi distending and occluding the finer arteries coursing the muscularis. Along one margin of the gallbladder was a firm cordlike structure about 2 cm in length, which on cross-section was seen to be a thickened, occluded vessel, from its position presumably the cystic artery. The thickness of the wall of the gallbladder was increased owing to edema, mainly of the muscularis, which was the seat of the thrombotic nodules described in the foregoing. The mucosa, which was intact and normally smooth, was covered in its proximal half by a dark brown, somewhat viscid material probably representing an admixture of bile and altered blood. When the mucosa was washed free, it appeared pale except for scattered dark blue spots shining through its surface similar in appearance to and corresponding in location with the subserous nodules which have been described. No bleeding point was demonstrable. The clotted blood consisted of one mass which formed a cast of the distal half of the gallbladder and several other disorganized smaller pieces. The peripheral portion of the large clot was rather dry and pinkish red, the central part a deep purplish red. A lymph gland measuring 1 by 1 by 0.5 cm attached to the proximal portion of the gallbladder was fleshy pink, soft and enlarged.

The microscopic description of a section through one of the bluish red nodules reads: There was a marked disproportion between the size of the channel and the thickness of the vascular wall, apparently due to an aneurysmal dilatation of the artery. The lumen was completely occluded by an organizing thrombus exceedingly rich in young granulation tissue and capillaries. Most of the vessel wall was destroyed rendering identification of the individual layers practically impossible. The outer layers of the vessel and the indefinitely demarcated surrounding fibrous tissue were infiltrated by round and plasma cells, together with a small number of leukocytes. A lymph gland taken from the region of the cystic duct showed a diffuse increase of lymphoid cells and large cortical follicles with distinct germinal centers.

The diagnosis submitted at the time was that of an infectious arteritis with multiple aneurysmal dilatations and consequent thromboses. It was not until later when the changes described in the foregoing were recognized as part of the pathologic entity—periarteritis nodosa—that the explanation of the bizarre symptomatology became apparent.

*CASE 2—History*—J. F. O'C., a man, aged 57, was admitted to the Cook County Hospital on Dec. 1, 1925, with complaints referable mainly to a decompensated heart. Shortness of breath, particularly marked on exertion, had been noted for eight months previous to admission. The swelling of his lower extremities had been noticed for only one month, whereas the scrotal edema which the patient presented became apparent the previous day. He also complained of dizziness on exertion, slight cough, and, occasionally, palpitation. Further questioning elicited the presence of nocturia. In the past history it was stated that the patient had had a grippal infection thirty years before and gonorrhea twenty-five years ago. The patient said that he had not had syphilis.

*Physical Examination*—This revealed a well nourished white man, somewhat dyspneic but not acutely ill. The temperature was 97 F., the pulse rate 100 and the respiratory rate 26. The blood pressure was 200 mm systolic and 100 mm diastolic. The heart was enlarged and the tones indistinct, but no actual murmurs were heard. Râles were audible at the bases of both lungs. The liver

extended two fingerbreadths below the costal margin and was tender, there was evidence of fluid in the abdomen and of a pitting edema of the lower extremities.

*Laboratory Observations*—The urine showed the presence of albumin and hyaline casts. The blood chemistry indicated some retention of the noncoagulable nitrogenous elements of the blood (nonprotein nitrogen 53.3, urea 66.96, and creatinine 2.75). The blood Wassermann test was negative, and the electrocardiographic tracing did not show any significant changes.

*Diagnosis*—The condition was considered an old nephritis with secondary hypertension and myocardial insufficiency.

*Subsequent Course*—Following the usual therapeutic measures the patient improved and he was discharged on Dec. 17, 1925, being referred for further observation and treatment to the heart clinic of the University of Illinois College of Medicine dispensary. After a month of ambulatory treatment, it was found necessary to hospitalize the patient on account of dyspnea.

*First Admission to Research and Educational Hospitals*—Except for the almost complete disappearance of dyspnea the patient in general presented the same picture described previously. His blood pressure at this time was recorded as 238 systolic and 128 diastolic. The nonprotein nitrogen was determined to be 110 mg. and creatinine 2.4. The Mosenthal test showed a variation of only two points in the specific gravity of the day specimens. The total day urine measured 471 cc. and the night urine 855 cc. with a specific gravity of 1.021. The phenolsulphonphthalein test showed an output of 15 per cent during the first half hour and a total output of 43 per cent in two hours. The urine showed a slight amount of albumin, an occasional granular and a few hyaline casts. The blood examination showed the presence of a secondary anemia with a leukocyte count of 11,400. The patient left the hospital after a stay of only four days but was readmitted on March 18, 1926.

*Second Admission*—The patient at this time presented symptoms similar to those previously noted. The blood pressure was recorded as 245 systolic and 130 diastolic. The heart tones were distant, but no irregularities or murmurs were heard. A slight edema of the scrotum was present. The phthalein test showed an output of 7 per cent of dye in the first hour and an additional 8 per cent in the second hour. The Mosenthal test yielded results similar to those recorded during the previous stay. The blood count on March 19, 1926, was 21,350 of which 83 per cent were polymorphonuclear leukocytes. The first record of abdominal complaint, which was subsequently and frequently repeated, was noted by the nurse on March 19. On the 21st, it was stated that the patient was restless and on the 27th delirium was at times manifested. On March 30, the patient developed severe pain in the right upper quadrant of the abdomen, which was described as cramplike, and was apparently excruciating. The picture presented suggested a surgical lesion, and consultation was requested.

The following notes dictated by the examining surgeon indicate the observations at that time: "There is spasm and some tenderness in the right upper quadrant chiefly. The abdomen is distended and held rigid. The patient is semidelirious and cannot be made to relax. Gallbladder disease is most likely present, although the possibility of appendicitis must be borne in mind. In view of the uncertainty of the diagnosis and the mental condition of the patient, further observation is desired and expectant treatment recommended."

On the following day the tenderness and rigidity had diminished but there was slight increase in the distention of the abdomen. A slight icterus appeared which vacillated in degree throughout the remainder of the course of illness. The patient was again seen about two weeks later by the surgeon who still felt inclined to defer operation, mainly on account of the mental condition of the patient. A previous flat film had shown no pathologic shadows in the upper right quadrant. Roentgenograms of the gallbladder region made on April 12

after the oral administration of sodiumtetraiodophenolphthalein did not show any definite gallbladder shadow. Repetition of the Graham-Cole procedure at a later date gave identical results.

The bromsulphalein test performed for a month at intervals of about one week showed the presence on the average of 30 per cent of the dye in the blood serum thirty minutes after injection. The icterus index determined April 1 was 25, and the van den Bergh test showed a direct positive reaction with the presence of 28 mg of bilirubin per hundred cubic centimeters of blood. On April 14, the icterus index had dropped to 11.5, the van den Bergh gave a diphasic reaction and quantitatively 18 mg per hundred cubic centimeters.

The patient became progressively weaker and developed, in addition to the evidences of nephritis, abdominal symptoms and delirium, definite signs of a polyneuritis. On May 15, it was noted that the patient had a wrist-drop on the left and a foot-drop on the right side, together with the inability to flex the index finger of the right hand. In the final stages he developed signs of fluid in the chest and abdomen, became more and more stuporous and passed into a deep coma on May 25, in which he died.

The temperature remained normal or subnormal until April 31, when 100.2 F was recorded on rectal measurement. Following this time the fever curve fluctuated irregularly, at no time rising above 101 F, usually averaging from 99 to 100 F. The curve frequently fell below the normal level, and on one occasion remained there for a period of three days. The pulse rate was at times disproportionately rapid, but for the most part its oscillations corresponded with those of the fever curve. The average pulse rate was between 100 and 120. Repeated blood counts showed the presence of a leukocytosis of variable degree. The white count rose from 20,000 at the time of entrance to 44,000 on April 2, to drop and rise again, and finally to fall once more to 19,000 recorded the day preceding death. Differential counts showed a polymorphonuclear leukocytosis ranging between 83 and 93 per cent, of which at no time did eosinophils constitute more than 2 per cent. The Wassermann test of the blood was negative. Blood cultures remained sterile.

Since the clinical facts in the case would not sustain any single diagnosis suggested and the combination of a number of different diseases seemed unlikely it was deemed advisable by the clinicians to be guilty of an error of omission rather than commission and to send the patient to autopsy with a diagnosis of morbus incognitus.

*Autopsy*—The autopsy was performed by Dr. R. H. Jaffe, from whose complete protocol the following excerpts were taken. In order to conserve space, only a brief summary of the essential observations made during the pathologic examination is included in this report.

The only alteration in the heart referable to the vascular disease was a thickening of the branches of the left circumflex coronary artery, with marked narrowing of the lumens of some. In order to detect these lesions it was necessary to examine the vessels with great care.

In the liver a network of scars was seen in the capsule, and on section, whitish linear markings separating unilobular and multilobular dark red areas were found. In the middle of the left lobe, 7 mm below the capsule, was a spherical, dark red nodule 9 mm in diameter, consisting of blood in the center surrounded by a grayish-white capsule.

Striking changes were found in the gallbladder (fig 1). On section of its wall, the enormously thickened cystic artery (*A*) was exposed to view. After removal of several pigment stones and a cloudy yellow bile, the lining of the gallbladder was seen to present a branching system of linear elevations (*B*) stained green mottled with yellow, representing apparently thickened blood vessels in which were foci of necrosis (*C*). In places, slight nodular enlargements were discerned. A few dark red hemorrhages were found in relationship to and distant from the involved vessels.

In the pancreas also the changes were remarkable. On section the pancreatic tissue was seen to be grayish-white with several subcapsular, more or less triangular dry opaque, yellowish-white areas (anemic necrosis), averaging about 8 mm in diameter often surrounded by firm grayish-red zones. In the fat tissue about the head of the pancreas the smaller arteries were thickened and their walls were firm and indurated.

The surface of the right kidney was uniformly granular, the regular grayish-white elevations being separated by deep grayish-red depressions. The cut surface was mottled grayish red and white, obliterating the normal renal markings. The medulla was pale as compared with the cortex. The sectioned vessels presented thickened walls and gaping mouths. The left kidney showed the same changes as the right and in addition, a yellowish-white, wedge-shaped subcapsular area about 5 mm at the base, located near the upper pole.



Fig 1—The opened gallbladder exposing a cross-section of the greatly thickened cystic artery (A) and a network of linear elevations (B) representing the thickened branches of the cystic artery. The lighter areas (C) are foci of necrosis corresponding to the sites of nodular thickenings.

Involving the vessels at the base of the brain was a marked sclerosis which extended also into the smaller branches.

The right peroneal and radial nerves on section showed no gross change. The intercarpal spaces on the dorsum of the right hand were conspicuous as compared with those of the left.

*Microscopic Report*—Areas of complete atrophy of the cortical tissue in the kidneys alternated with regions in which the parenchyma appeared uninvolved. In the more or less intact areas the glomerular tufts were rich in nuclear elements and the endothelial cells swollen, but the capillaries had distinct outlines and contained red blood cells, the tubules here were distended and lined by swollen, clear epithelial cells. In the zones of atrophy which assumed the form of striations not sharply demarcated from the relatively normal tissue, the glomeruli were hyalinized and the tubules diminutive or replaced by proliferat-

ing stroma rich in round cells. All the arteries from the interlobar branches to the arterioles showed changes, the most severe alterations, however, being noted in the atrophic areas. The walls of the interlobar arteries were greatly thickened, mainly owing to a diffuse connective tissue increase which obscured the normal distinction of the adventitial, medial and intimal coats. The lumina of these vessels were extremely narrow, being for the most part filled with fibrous tissue. In the adventitia there were dense collections of cells consisting chiefly of eosinophilic and neutrophilic leukocytes, round and plasma cells and histiocytes which infiltrated and extended into the surrounding tissues. Similar changes and more acute alterations were observed in the arcuate arteries. Here one saw fibrinoid necrosis of circumscribed parts of vessel walls often

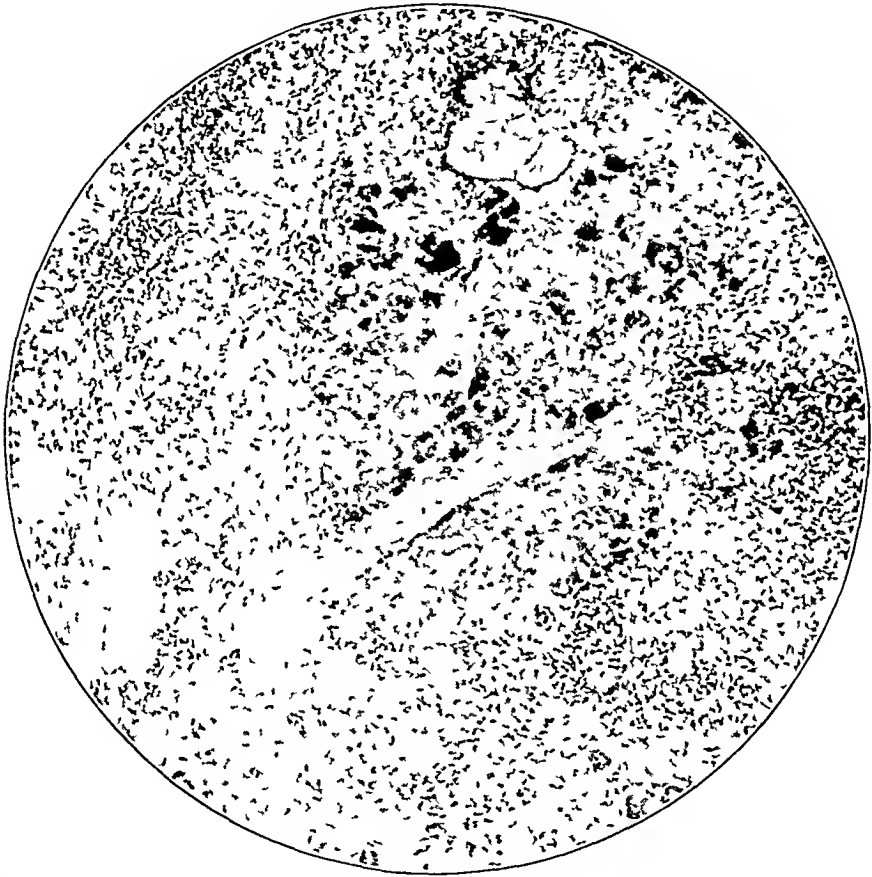


Fig 2—Circumscribed necrosis of the pancreatic parenchyma surrounded by a zone of inflammatory reaction  $\times 80$

involving the internal elastic membrane, remnants of which could still be identified. In some places, presumably the sites of origin of the interlobular branches, the walls were entirely necrotic. Here and there the infiltrations of eosinophils extended toward the inner coats of the vessel walls. The arterioles showed extreme hyaline thickening with deposition of lipoid. In the larger arteries the occlusion was apparently due to organized thrombi showing distinct canalization, whereas the medium sized and smaller arteries were narrowed as a result of proliferative changes of the intima.

There were circumscribed areas of necrosis in the pancreas in which the acini and fat cells were transformed into structureless masses. Each one of these foci of necrosis (fig 2) were surrounded by a zone of inflammatory

reaction containing many eosinophilic leukocytes, round and plasma cells and fibroblasts. The acini in the region of reaction had lost their structure and the individual parenchymal cells their zymogenic granulation. There were also areas of scar formation, the fibrous tissue being cellular and containing shrunken epithelial cells filled with fat droplets. There was a normal preservation of the islets of Langerhans, the cells of which contained small fat granules. The arteries coursing through the thickened interlobular septums were markedly altered by a noteworthy intimal proliferation which had led to high grade, more or less eccentric narrowing of the lumina with at times irregular canalization (fig 3). In some areas more recent changes represented by infiltrations of eosinophilic leukocytes and round cells were noted (*a*). These infiltrates, which

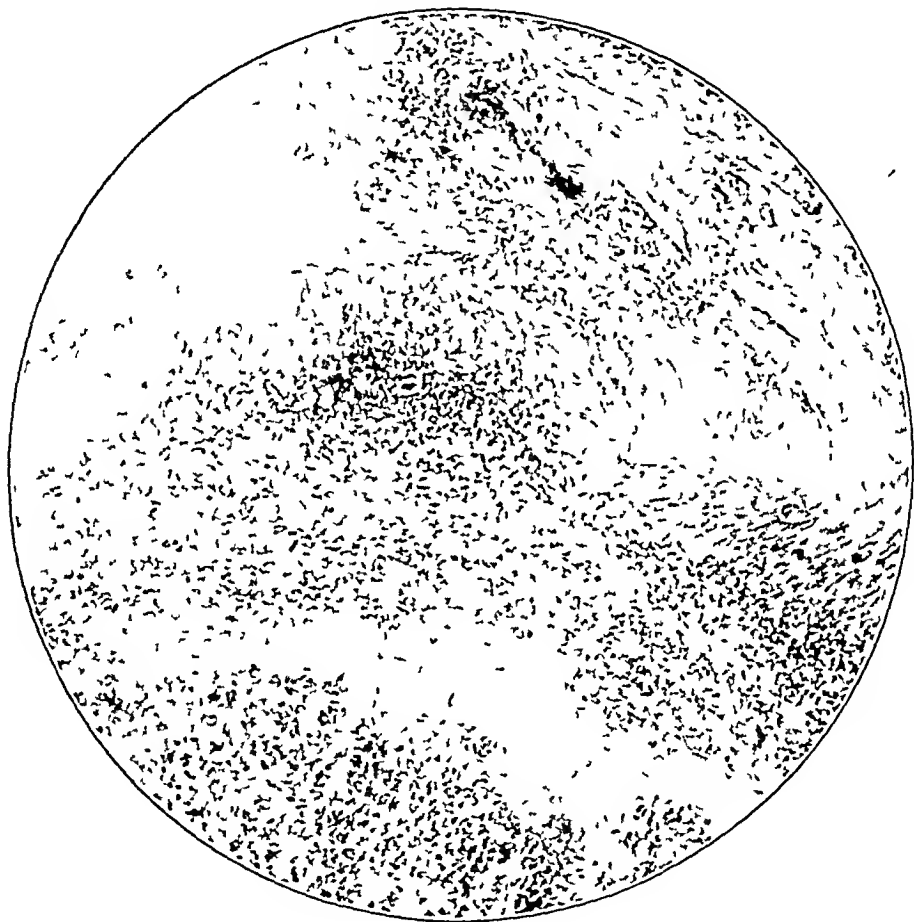


Fig 3—Irregular canalization of a medium-sized pancreatic artery. The periarterial infiltration is most marked at (*a*) where the inflammatory cells appear to extend from the adventitia (*b*) to invade the media (*c*).  $\times 60$

appeared to have their origin in the adventitia and to have progressed toward the media, may have involved the entire circumference of the smaller arteries. In places circumscribed aneurysmal dilatations filled with blood clots were found adjacent to vessels the lumina of which were almost completely occluded.

The wall of the cystic artery (fig 4), which was severely injured, was greatly thickened and its caliber correspondingly decreased. About one third of the lumen was occupied by a loose network of fibrin (*a*), in the meshes of which a number of leukocytes mostly with eosinophilic granulations were found. That portion of the internal part of the vessel wall immediately adjacent to the fibrinous deposit was composed of a coarse hyaline substance (*b*) which was limited to this area. In passing centrifugally, the hyalinized zone was found to

be separated from the external portions of the vessel wall by a cavity (*c*) (recanalization?) which was lined in the peripheral part by foamy cells (*d*) with golden yellow pigment granules (hematoidin in macrophages). In the remaining two thirds of the wall, a part of which is shown in figure 5, the internal layers consisted of fibrillar connective tissue, the fibers being arranged concentrically about the lumen (*a*). In the more peripheral layers, remnants of the elastica interna represented by a tortuous line (*b*) often broken up by the invading connective tissue could be identified. All that remained of the media (*c*) were a few smooth muscle fibers with thin elastic fibrils between them attached to the external surface of the inner elastic membrane. The enormously thickened adventitia (*d*) passed almost imperceptibly into the surrounding fibrous tissue (*e*).

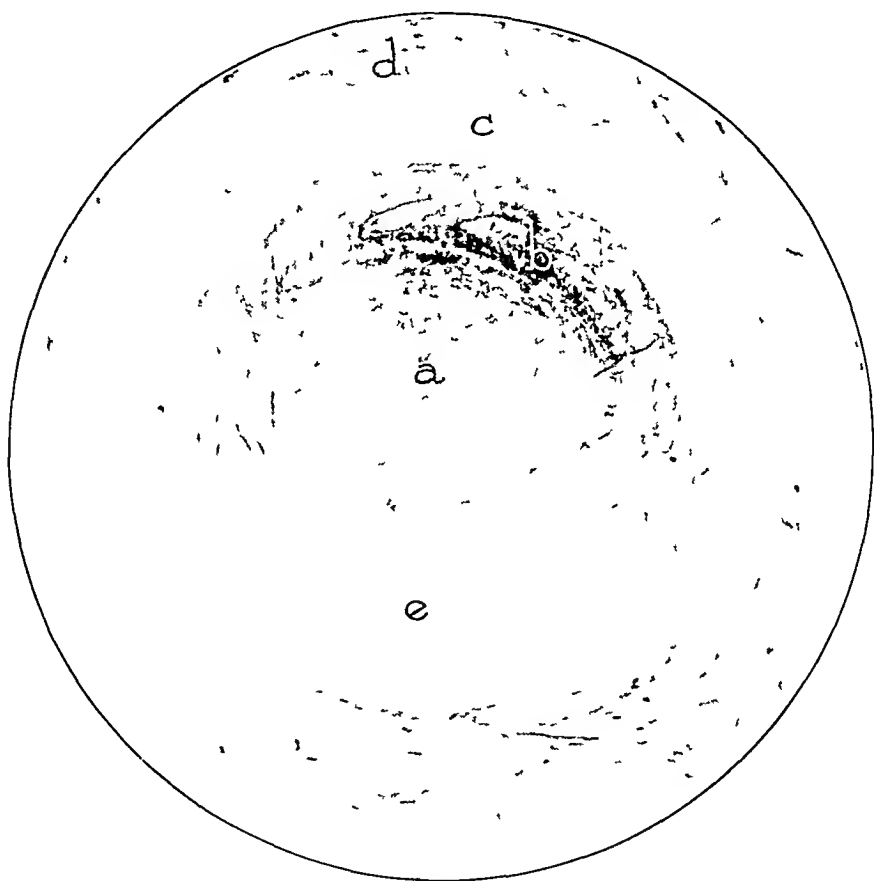


Fig 4—The greatly thickened wall of the cystic artery in cross-section. The present small lumen is partially occupied by a loose network of fibrin (*a*) in the meshes of which are many leukocytes. Adjacent to the fibrinous deposit is a coarse hyaline substance (*b*), external to which is a cavity (*c*) lined by macrophages (*d*) laden with hematoidin. The site represented in figure 5 is located at (*c*)  $\times 24$ .

In the liver, the periportal connective tissue was increased in amount and tended to invade by extension the adjacent portions of the surrounding lobules. Infiltrations of cells were marked in these areas, as was also bile duct proliferation. The branches of the hepatic artery in general had suffered little injury. The nodule in the left lobe noted in the gross description consisted of a blood coagulum surrounded by a connective tissue capsule. The clot had a homogeneous hyaline center in which were embedded a few macrophages and

leukocytes the latter mainly oxyphilic. Peripherally there were fibroblasts and young capillaries, together with a greatly increased number of macrophages which contained a dark, yellowish-brown, blood pigment. The capsule consisted chiefly of fibrillar connective tissue and distended capillary vessels with in one place a few degenerated smooth muscle fibers. In the more external layers were found well circumscribed, small foci of infiltrated round cells and eosinophilic leukocytes. The nodule was embedded in a dense connective tissue supporting several medium sized arteries with thick walls and narrow lumina.

The most conspicuous change in the prostate was found on cross-section of an artery (fig 6) which was of far greater caliber than would correspond to the thickness of its wall. The lumen of the vessel was apparently distended by a blood clot

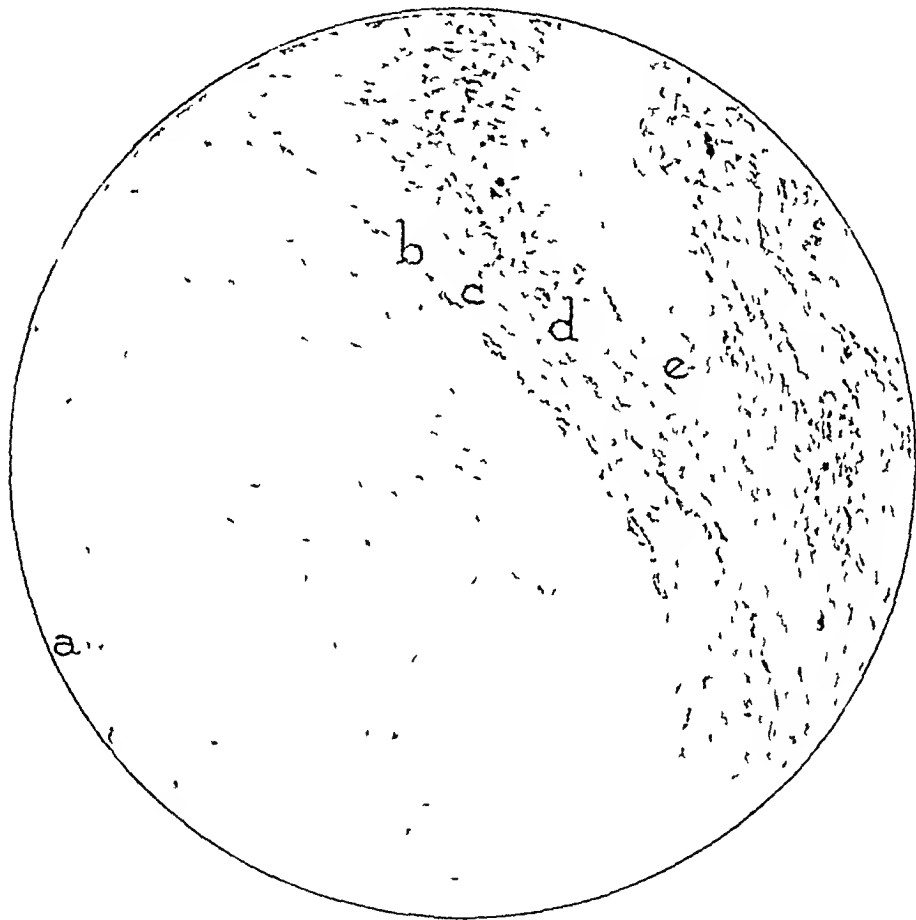


Fig 5—A higher magnification of that portion of the wall of the cystic artery designated by (c) in figure 4 (Weigert's elastica stain). About the lumen (a) are concentric layers of fibrillar tissue, in the more peripheral parts of which are remnants of the elastica interna (b). The media (c) is partially destroyed but can still be identified. The enormously thickened adventitia (d) passes almost imperceptibly into the surrounding fibrous tissue (e).  $\times 60$

interlaced with young capillaries and fibroblasts. Immediately about the artery there was considerable deposition of blood pigment both free and engulfed, and in close proximity (not included in the illustration) were several other thick-walled, almost completely occluded vessels separated by dense connective tissue containing pigment.

Many of the larger arteries of the heart did not show any change, although some revealed proliferation of the intima producing eccentric narrowing of the vascular channels. In the connective tissue about the vessels and in the sub-

epicardial fat tissue were circumscribed infiltrations composed of lymphoid cells and eosinophils, which extended between the muscle fibers

In some of the bundles of the peroneal nerve evidence of severe injury was found. The myelin sheaths of the nerve fibers stained bright orange with sudan III, and in some places were broken up into droplets of varying sizes which were partly phagocytosed by histiocytes. The small arteries here had diffusely thickened walls surrounded by round cells which frequently invaded the outer coats of the vessel.

Hemorrhage and necrosis associated with the presence of severe vascular injury was noted in the testicle. In the areas of greatest involvement could be seen a diffuse fibrinoid degeneration with cellular infiltrations of the arterial walls and thrombosis of the lumina.

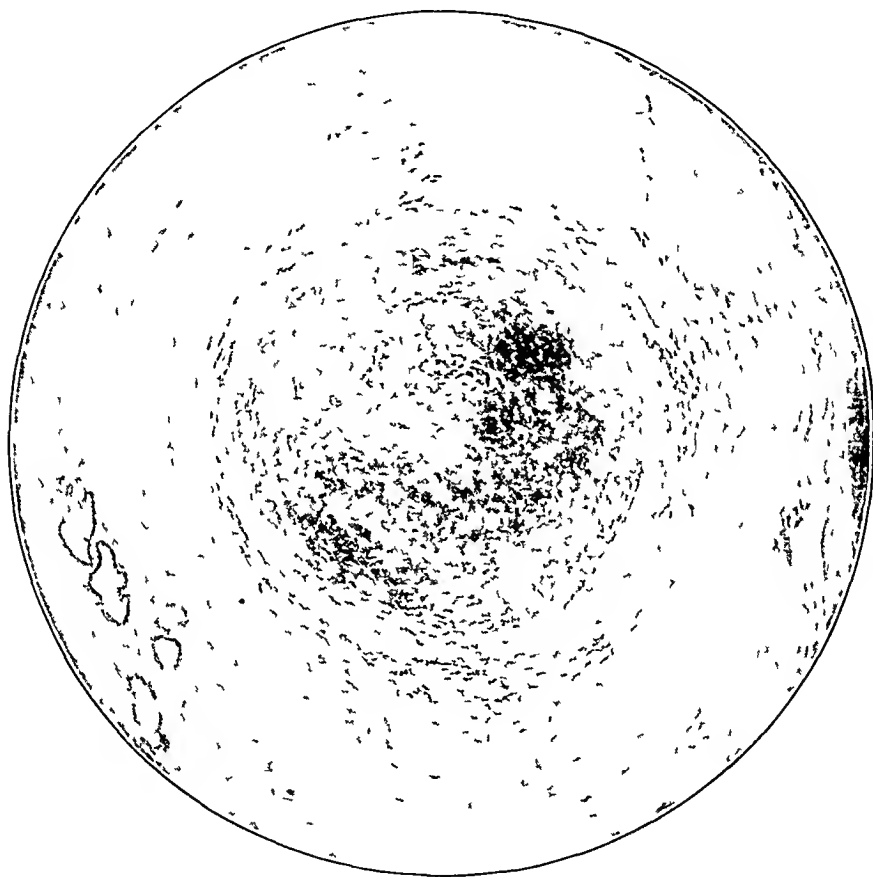


Fig 6—Section through a thrombosed aneurysmal outpouching of a prostatic artery. About the vessel wall is a heavy deposit of blood pigment both free and engulfed.  $\times 36$

In the fat tissue surrounding the suprarenal and the fibrous tissue about the thyroid were striking alterations in the blood vessels, around which were nodular accumulations of round cells and eosinophilic leukocytes. Within these glands the changes affecting the arteries were less marked.

In the spleen, the malpighian bodies presented distinct germinal centers, while the pulp showed diffuse thickening of the reticulum and sinuses of medium width filled with blood. In the trabeculae were many eosinophils and plasma cells. The walls of the smaller arteries were sclerotic and hyalinized.

The vessels in the brain were extensively involved by atherosclerosis presenting, even on careful search, no evidence of inflammatory change.

## ETIOLOGY

A great deal of interest has centered about the etiology of the malady. A consideration of the evidence pro and con in connection with various views is beyond the scope of this paper. It is generally agreed, however, that periarteritis nodosa is an infectious disease, although the causal organism has not been identified. Investigations carried on in connection with a corresponding condition occurring in deer has failed to shed any light on the causation of the disease (Lupke,<sup>26</sup> Jaeger<sup>27</sup>). The study of similar cases in a calf (Guldner<sup>28</sup>) and a pig (Joest<sup>29</sup>) likewise led to negative bacteriologic results. Cameron and Ludlow<sup>13</sup> suggest a parasitic origin on the basis that multiple aneurysms occurring along the mesenteric vessels in horses is known to be due to the parasite *Strongylus armatus*. What is more significant, these authors state, is a case of aneurysms in dogs studied by Haythorn and Ryan,<sup>30</sup> in which it apparently was established that the aneurysms were produced by a nematode worm, *Spuroccerca sanguinolenta*. The eosinophilia found at times in man in periarteritis nodosa may be a point in favor of the parasitic theory.

Harris and Friedrichs<sup>11</sup> (who give a complete summary of the etiology of periarteritis nodosa) have succeeded in reproducing lesions in rabbits similar to those occurring in man, and have adduced a great deal of evidence in support of their claim that a filterable virus is the cause of the disease. In his latest review of periarteritis nodosa, Gruber,<sup>4</sup> after weighing the facts thus far accumulated, stoutly defends the notion that this condition is not a disease *suu generis*, but that it may be produced by a number of different agents, a view shared by most authors. It is the general consensus of opinion that syphilis plays no rôle in the production of the disease, it is therefore no longer accorded a place of importance in discussions of the subject.

## PATHOLOGY

Since the nature of the disease as already stated is, as a rule, first recognized at the time of autopsy, opportunity for clinical study of periarteritis nodosa has been limited, whereas the pathologic side of the

26 Lupke, F. Ueber Periarteritis nodosa bei Aushirschen, Verhandl d deutsch path Gesellsch **10** 149, 1906

27 Jaeger, A. Vergleichend—pathologische Untersuchungen ueber die Periarteritis nodosa, Verhandl d deutsch path Gesellsch **13** 209, 1908

28 Guldner, E. Zwei neue Beobachtungen von Periarteritis nodosa beim Menschen und beim Hausrinde, Virchows Arch f path Anat **219** 366, 1915

29 Joest, referred to by Guldner (footnote 28)

30 Haythorn, S. R., and Ryan, A. H. Aortic Aneurysms in Dogs with the Report of Six Cases, J. M. Research **35** 411, 1916-1917

31 Harris, W. H., and Friedrichs, A. V. The Experimental Production of Periarteritis Nodosa in the Rabbit with a Consideration of the Specific Causal Excitant, J. Exper. Med **36** 219, 1922

subject has been considered in an exhaustive manner in numerous recent works (Giubet <sup>4</sup>) In view of the abundant literature, a detailed discussion of the morbid anatomy of the disease would prove superfluous For a clear understanding, however, of the complicated symptomatology, it seems desirable to give briefly the essential anatomic changes which characterize the malady

The schematic chart drawn by Harris and Friedrichs <sup>23</sup> admirably conveys to the reader in sequence the processes involved in the pathologic consideration of periarteritis nodosa

*Group 1 Injury to Vessel Wall*—This group represents the true primary lesion occurring in the arterial wall It is characterized by exudative and degenerative processes present in the periadventitial structures, the adventitia and the media and occasionally in the intima Acute, subacute and chronic inflammatory elements may be present, also degenerative changes characterized especially by marked necrosis of the media

*Group 2 Results of Wall Injury*—Group 2 presents the phenomena attendant on severe wall injury as manifested by aneurysms, both true and false, hemorrhagic extravasations which may be the immediate cause of death and extensive thrombosis and infarction In this group especially are the proliferative and reparative processes noted and at times organization of the thrombi These various occurrences are the result of group 1

*Group 3 Injury of Tissue or Organs*—Herein are considered the retrograde changes present in the organs These changes may be attributable to the curtailment of blood supply by the thrombosis present in group 2 or to pressure injury from the hemorrhagic extravasation Cloudy swelling, fatty degeneration, coagulation necrosis or other forms of cell destruction are observed The hemiplegia, diarrhea, nephritis and other clinical phenomena may be included in this group, which is consequent to the pathologic processes present in group 2

Particular cognizance should be taken of the result of the damage to a vessel wall, especially the aneurysmal dilatation which is at times followed by rupture and consequent hemorrhage One should also bear in mind that the periarteritic node is often an aneurysmal out-pouching rather than a mass of proliferated granulation tissue projecting from one side of a vessel wall As a matter of fact, a modification of the term introduced by Kussmaul and Maier <sup>1</sup> suggested by Harris and Friedrichs, <sup>23</sup> namely, periarteritis nodosa aneurysma thrombotica, furnishes a more accurate description of the characteristic changes The lesions are not of a nodose form in all cases, for diffuse thickening of the entire vessel wall is not infrequently encountered, nor are macroscopic nodose or diffuse thickenings constant accompaniments of the disease

A complete absence of grossly demonstrable vascular lesions were found in the cases of Meyer,<sup>32</sup> Veszpremi<sup>33</sup> and Wohlwill,<sup>34</sup> although the microscopic changes were typical

#### SYMPTOMATOLOGY

The basis of the symptoms can be readily grasped when one remembers that periarteritis nodosa, being essentially a disease of the medium-sized blood vessels, resembles, from the standpoint of the widespread distribution of the susceptible tissues, such conditions as syphilis and arteriosclerosis. The bewildering symptomatology of the disease can be rendered least intricate by assuming the presence of an infectious process which in addition to producing general disturbances such as fever, tachycardia, prostration, cutaneous eruptions and leukocytosis, causes symptoms based on circulatory disturbances in the systems or regions affected. On this basis Kroetz<sup>35</sup> divides the clinical manifestations of periarteritis nodosa into two groups—constitutional and local. In the first group the symptoms are indistinctive, being those of a chronic septic process with an onset which may be acute, but which is more often insidious. The temperature is irregular and mostly subfebrile, but may reach 104 or even 105 F. A remittent type of fever is not infrequently noted, the remissions at times being associated with drenching sweats. Afebrile periods are not uncommon. Rigors are exceptional, although chilliness is sometimes present. The pulse is, as a rule, disproportionately rapid even in the absence of evidence of cardiac involvement. A most conspicuous feature is a high grade secondary anemia which, when associated with progressive asthenia and emaciation, gives the patient the appearance referred to in the original description of the disease by Kussmaul and Maier<sup>1</sup> as chlorotic marasmus. The white cell blood count is as a rule increased, being generally between 15,000 and 30,000, at times showing a marked eosinophilia which may reach 51 per cent (Lamb<sup>20</sup>). The purpura especially involving the skin which is at times noted is apparently the result of the general infection. Cutaneous eruptions of various descriptions are encountered, including urticarial crops, erythema nodosum and forms described under the term purpura rheumatica.

The second group of symptoms in Kroetz' division, that is, those due to local vascular changes, are generally classified according to the

32 Meyer, P. S. Ueber die klinische Erkenntnis der Periarteritis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl klin Wchnschr **58** 473, 1921

33 Veszpremi, D. Ueber die Periarteritis nodosa, Beitr z Path Anat u z allg Pathol **52** 476, 1912

34 Wohlwill, F. Ueber die nur mikroskopisch erkennbare Form der Periarteritis nodosa, Virchows Arch f path Anat **246** 377, 1923

35 Kroetz, C. Zur Klinik der Periarteritis nodosa, Deutsches Arch f klin Med **135** 311, 1921

system involved In an excellently organized summary of the literature until 1899, von Schrotter <sup>36</sup> segregated the polymorphic manifestations of periarteritis nodosa into a number of clinical types, including renal, abdominal, neuromuscular, cardiac and bronchial It is essential, however, to bear constantly in mind the fact that, as a rule, several systems are simultaneously affected, limitation of symptoms referable to one organ being exceptional

Although the coronary arteries are involved more frequently than any other set of vessels, cardiac symptoms are notoriously absent Precoordial pain is exceedingly rare, a noteworthy fact in view of the present current hypotheses with reference to the causation of angina pectoris The cardiac decompensation which not infrequently occurs can most often be explained as secondary to kidney damage The blood pressure is high in the presence of nephritis only

Involvement of the kidney is so obstrusive in the clinical picture of the disease as to merit the major consideration in the article by Keegan <sup>24</sup> and in one of Gruber's <sup>37</sup> reports In addition to the widespread arterial changes there is frequently extension of the periarteritic inflammation into the interstitium of the kidney, at times associated with a hematogenous glomerulonephritis (Ophuls <sup>3</sup>) Death due to uremia, as in both instances reported in the foregoing, is not an uncommon termination of the disease Pain in the loin, especially in association with a ruptured aneurysm of the renal artery or its branches causing extensive perirenal hemorrhage, may be a forerunner of death

Abdominal symptoms, especially those referable to the gastrointestinal tract, are almost always present Within the abdomen in order of frequency, the gastro-intestinal canal, kidneys, liver and gall-bladder, spleen, pancreas, spermatic artery, diaphragm and suprarenals are affected by arterial changes Since involvement of any one of the aforementioned structures may produce pain, it is not surprising that this symptom is by far the most frequent of the abdominal manifestations In the presence of multiple lesions, which is the rule, it is difficult and at times impossible to designate definitely which one is responsible for the production of pain The pain is often extremely severe, described mostly as colicky and at times as tearing In the majority of cases it is located in the upper part of the abdomen, especially in the epigastrium, while in the remainder it tends to be diffuse Vomiting is mentioned at some time during the course of the disease, as is also anorexia, in more than half the reports Diarrhea or consti-

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36 Von Schrotter, L Ueber Periarteritis nodosa, Wien klin Wchnschr **12** 404, 1899

37 Gruber, G B Zur Frage der Periarteritis nodosa, mit besonderer Berücksichtigung der Gallenblasen-und Nieren-Beteiligung, Virchows Arch f path Anat **258** 443, 1925

pation alone may be prominent, or the two may alternate. Melena is occasionally recorded. Peritonitis, the result of a local infarction with ulceration and perforation of the bowel, is one mode of death described. The abdominal symptoms may appear in irregular combinations and not infrequently present the picture of an acute surgical condition (discussed in the following).

A most troublesome and refractory condition is presented by involvement of the branches of the peripheral arteries. Symptoms of polyarthritis simulating the ordinary acute rheumatic fever or pains in the muscles, often of a far more excruciating nature, are encountered in most cases during the course of the disease. Involvement of the branches supplying the peripheral nerves leads to symptoms of a progressive multiple neuritis which may dominate the clinical picture. According to Wohlwill,<sup>38</sup> the degenerative changes in the nerves may result from the general toxemia independent of the changes in the arteries of the affected nerves. A recent review of the neurologic aspect of the disease is well presented by Balo.<sup>39</sup> In contradistinction to the frequency of peripheral nerve involvement, the vessels of the central nervous system are only exceptionally affected. The localization within the brain is associated with grave significance on account of the tendency of the disease to produce thrombosis and aneurysmal dilatation with rupture and hemorrhage.

The formation of nodules in connection with the cutaneous vessels is of great importance from a diagnostic standpoint. The nodes may represent either granulomatous thickenings or, as is more often the case, thrombosed aneurysmal dilatations. Rupture of the saccular outpouchings may lead to cutaneous hematomas. Along the course of the palpable arteries, such as the brachial and temporal, at times chains of nodules are felt.

The less common localizations not mentioned in the foregoing include the bronchial and exceptionally the pulmonary arteries (involvement of the bronchial mucous membrane apparently causing asthmatic symptoms is reported by Ophuls<sup>3</sup>), the generative organs and serous membranes.

Of particular interest to the clinician is the symptom complex generally referred to as "acute surgical belly." Pain, vomiting, tenderness, rigidity, fever and leukocytosis are not infrequently combined during the course of periarteritis nodosa, but as a rule are due to nonsurgical lesions. As a matter of fact, the average case of periarteritis

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<sup>38</sup> Wohlwill, F. Aerztlicher Verein zu Hamburg, Sitzung vom 4 Dez., 1917, Berl klin Wchnschr **55** 94, 1918.

<sup>39</sup> Balo, J. Ueber eine Haufung von Periarteritis nodosa. Fallen nebst Betragen zur Polyneuritis infolge von Periarteritis nodosa, Virchows Arch f path Anat **259** 771, 1926.

nodosa with abdominal symptoms constitutes a surgical *noli-me-tangere*. On the other hand, it is not altogether rare to meet with a complication of a vascular involvement in which operative intervention is imperative. One finds reports of cases, for instance, in which perforation of an intestinal ulcer, the result of infarction of the bowel, or alarming abdominal hemorrhage from a ruptured aneurysm has occurred. The task of differentiating between the surgical and the nonsurgical abdominal manifestations in a case of periarteritis nodosa, particularly when the condition is not recognized, is obviously a difficult one. The abdominal aspect, which has hitherto received but little emphasis in the literature, seems to warrant elaboration not only because of its diagnostic importance to both internist and surgeon, but also because it furnishes a valuable aid in the diagnosis of the disease if exploration is undertaken.

The abdominal conditions which periarteritis nodosa may simulate are numerous. In cases in which symptoms in the upper part of the abdomen are present, gallbladder disease, ruptured peptic ulcer or acute pancreatitis are usually considered, whereas with symptoms in the lower part of the abdomen, appendicitis is most often suspected. In a number of instances the picture presented is so perplexing that no attempt is made to diagnose the case preoperatively. Occasionally the onset of the disease is abrupt with acute abdominal manifestations, in which case the underlying condition is seldom if ever suspected. As a rule, however, the onset is insidious, and the abdominal manifestations occur in association with other more or less obscure symptoms and constitute only part of the complex clinical picture. Acute abdominal symptoms occurring in the presence of combinations of various syndromes, such as polyneuritis, polymyositis and nephritis, lead to further confusion when periarteritis nodosa is not suspected.

In both of the aforementioned case reports, upper abdominal pain and jaundice directed attention to disease in the biliary tract. In the first case the signs pointing to gallbladder disease led to a cholecystectomy and temporary improvement. The disease process, however, was not recognized at the operating table. The second patient would likewise have been subjected to a laparotomy had not the presence of delirium deterred the surgeon from undertaking immediate operation. Gruber<sup>37</sup> recently described a case in which cholecystectomy was performed following the diagnosis of gallbladder disease. Grossly the extirpated organ presented no evidence of periarteritis nodosa. Microscopic sections, however, showed typical changes in the branches of the cystic artery. The patient died later with symptoms of uremia, and was found to have the characteristic periarteritis lesions in the kidneys. In the first of two cases described in the contribution by Klotz<sup>21</sup> a diagnosis of empyema of the gallbladder was made, based on signs of sepsis and acute abdominal symptoms. At the autopsy the cystic artery was found

to be thickened and thrombosed. However, the recurrent abdominal pain was presumably the result of rupture of several intrahepatic aneurysms, one of which had led to a subcapsular extravasation followed by intraperitoneal hemorrhage and death. A similar case, the third in Christeller's report with symptoms leading to a diagnosis of cholecystitis, ascending cholangitis or pancreatic apoplexy, came to autopsy with observations of multiple periarteritic nodes in the liver and a ruptured aneurysm on the under surface of the right lobe with hemoperitoneum. The gallbladder was filled with a blood coagulum similar to that found in the first case described in this paper, and here also no bleeding point was found. Chiari's<sup>40</sup> case of ruptured aneurysm of the cystic artery, cited as an unrecognized example of periarteritis nodosa by Gruber,<sup>37</sup> was an instance of aneurysm per erosionem due to an ulcerative cholecystitis unassociated with periarteritic changes.

The severity of the upper abdominal pain can be so marked as to suggest a ruptured peptic ulcer or pancreatitis. Mertens<sup>9</sup> describes a case in which the symptoms interpreted as those of an acute perforation led to an exploration and the discovery of slight pancreatic necrosis. The patient was exhibited during convalescence as having a classical example of acute pancreatitis. At postmortem a bilateral perineal hematoma was found which in all likelihood was responsible for the acute manifestations. A similar picture was presented in the case of Laux.<sup>41</sup> The diagnosis of pancreatitis was made also in the case described by Muller.<sup>42</sup>

As might be anticipated, when the pain is experienced in the lower part of the abdomen, involvement of the appendix is suspected. In the second case of periarteritis nodosa described by Lamb,<sup>20</sup> a girl, aged 10, with lower abdominal symptoms, was operated on for acute appendicitis. At the laparotomy the appendix and peritoneal cavity were found to be normal, and no cause for the symptoms was discovered. Ophuls<sup>8</sup> cites an instance of periarteritis nodosa in a man, aged 38, who one week after the onset of his symptoms, which included severe abdominal pain, underwent an operation for appendicitis. He obtained only temporary relief.

Benedict's<sup>43</sup> case is an excellent illustration of the diagnostic dilemmas in which abdominal symptoms in cases of periarteritis nodosa place even the most experienced clinicians. A woman, aged 44, with a presumptive diagnosis of appendicitis, was transferred from the med-

40 Chiari, H. Berstung eines Aneurysmas der Arteria cystica in die Gallenblase mit tödlicher Blutung, *Prag med Wchnschr* 8 33, 1883.

41 Laux, F. J. Periarteritis nodosa, *Mitt a d Grenzgeb d Med u Chir* 38 582, 1925.

42 Muller, H. Referred to by Gruber (footnote 37).

43 Benedict, H. Ueber Periarteritis nodosa, *Ztschr f klin Med* 64 405, 1907.

ical to the surgical clinic on account of severe abdominal pain and the presence of a tumor mass in the appendiceal region. In the surgical ward the pain and swelling were found to be due to a hemorrhage in the abdominal wall which did not require surgical intervention. The development of jaundice and fever within the following two weeks might have led to a diagnosis of cholelithiasis had not the presence of subcutaneous nodules suggested a malignant condition. The patient was returned to the medical department, where excision of a nodule proved the condition to be periarteritis nodosa.

In the majority of cases, although the condition is considered surgical, a definite preoperative diagnosis is not ventured. Abdominal pain, fever and leukocytosis aroused the suspicion of a focus of abdominal suppuration in the case of Manges and Baehr.<sup>22</sup> At the operation the presence of the characteristic nodules along the course of the mesenteric vessels led to recognition and the diagnosis by the surgeon (Buerger) of periarteritis nodosa. Microscopic examination of a nodule removed for biopsy confirmed the opinion of the surgeon. So far as can be ascertained from the literature, this is the only case in which the diagnosis of periarteritis nodosa was confidently and correctly made at the operation table. In the case described by Keegan,<sup>21</sup> an exploratory operation was performed for symptoms referable to the right upper quadrant. The abdominal organs were normal, whereas exploration through a right flank incision disclosed a diseased kidney which was proved later to be the seat of periarthritic changes. In the case reported by Lemke,<sup>44</sup> an 11 year old boy was examined on account of abdominal symptoms. Except for the presence of a large amount of clear fluid, the abdomen was free from change. Four weeks later the child suddenly went into collapse, and died in a few minutes. The autopsy revealed in addition to lesions elsewhere a walnut-sized, perforated hematoma on the under surface of the liver. Repeated violent attacks of right hypochondriac pain led to the transfer of the patient in the case of Harris and Friedrichs<sup>23</sup> to a surgical ward, where an operation was deemed inadvisable on account of the poor condition of the patient. At autopsy, in addition to the nodular formations involving branches of the coronary, renal and gastro-epiploic arteries, there was a ruptured aneurysm of a kidney vessel with extensive hemorrhage into the circumrenal tissues. A group of puzzling cases with abdominal manifestations is illustrated by a case reported by Meyer,<sup>32</sup> in which the polyneuritic symptoms were in the foreground, although the patient complained also of gastric disorder and bloody stools, among other symptoms. On the day of death, abdominal pain, tenderness and rigidity were most prominent. At

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44 Lemke, R. Ein Beitrag zur Frage der Periarteritis nodosa, *Virchows Arch f path Anat* **240** 30, 1922

autopsy an acute suppurative peritonitis, the result of perforation of one of the multiple disseminated ulcers of the small bowel, was discovered. The frequency of intestinal ulceration is indicated in the review of twenty cases by Meyer,<sup>32</sup> in ten of which defects of the wall were present.

#### DIAGNOSIS

The diagnosis of periarteritis nodosa in the absence of the characteristic cutaneous nodules or operative intervention is seldom correctly made. Based on the predominating symptom complex in the clinical picture, the diagnosis is usually that of sepsis, military tuberculosis, typhoid, trichiniasis, nephritis, an acute abdominal condition requiring surgical intervention, dysentery, polyneuritis, polymyositis, dermatomyositis, meningitis, encephalitis, cerebral hemorrhage, purpura or one of many other more or less well recognized conditions. As Lamb<sup>30</sup> points out, the aforementioned diagnoses are practically always made with reservations, since the clinical picture is, as a rule, atypical, furthermore, no one disease in the aforementioned group can account satisfactorily for all the symptoms usually manifested. The latter statement is borne out particularly in the abdominal group, in which, associated with the acute symptoms, are signs of extra-abdominal disease such as nephritis, polyneuritis, purpura and other conditions which cannot be logically explained by any primary surgical abdominal lesion.

The difficulty in recognizing the disease in the absence of visible lesions, aside from its rarity, is due not only to the multiplicity but also to the innumerable combinations of the symptoms. From his study of the literature, Meyer<sup>32</sup> considered the following triad of clinical syndromes of importance in the diagnosis of periarteritis nodosa: chlorotic marasmus, polyneuritic and polymyositic symptoms, and gastro-intestinal manifestations. To this triad, later writers are agreed (Brinkmann,<sup>45</sup> Christeller<sup>6</sup>) that nephritis should be added as a cardinal symptom. Benefiting from the experience with his first case in which the disease was first recognized at autopsy, Sack<sup>25</sup> was able to predict, from the clinical symptoms described, the presence of periarteritis nodosa in a second case in which nodules were at no time discovered.

The appearance of nodules in the skin, present at one time or other in approximately 20 per cent of the cases, as a rule furnishes the first clue to and not infrequently leads to the discovery of the nature of the disease. In some cases the suspicion of the presence of periarteritis nodosa based on the clinical symptomatology causes a more careful search to be made, which is at times rewarded by the finding of the characteristic lesions. The occurrence of cutaneous granulomas and

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<sup>45</sup> Brinkmann. Zur Klinik der Periarteritis nodosa, München med Wchnschr 69 703, 1922.

aneurysmatic nodes not only allows early clinical recognition of periarteritis nodosa, but also permits, through vital excision, microscopic confirmation and proof of the presence of the disease. Through biopsy the existence of periarteritis nodosa (in some instances suspected before histologic examination) was unequivocally established in the cases of Kussmaul and Maier,<sup>1</sup> Schmorl,<sup>16</sup> Benedict,<sup>43</sup> von Haun,<sup>47</sup> Morawitz,<sup>48</sup> Kopp,<sup>49</sup> Carling and Hicks,<sup>14</sup> and Weigeldt.<sup>50</sup> Not all cutaneous or subcutaneous swellings occurring in the course of periarteritis nodosa present the typical changes, however, as observed in the case of Klotz,<sup>21</sup> in which a nodule on becoming fluctuant was incised and yielded a thick gelatinous material. It may be well to point out also in this connection that not all nodules along the course of superficial arteries are part of a true periarteritis nodosa, as exemplified by the case of Sabin<sup>16</sup> mentioned in the introductory remarks.

The revelation of the characteristic lesions in cases in which cutaneous nodes are absent occurs in instances in which operative intervention is undertaken, usually on the basis of a mistaken diagnosis. In the case of Manges and Baehi,<sup>22</sup> the surgeon Buerger recognized the distinctiveness of the lesions along the mesenteric vessels, and confirmed his opinion by excision and microscopic examination of one of the nodes. A painful swelling involving the right calf of their patient prompted Carling and Hicks<sup>14</sup> to explore the lesion. The "lumpiness" was due to a number of scattered nodules about the small arteries of the muscles associated with the presence of edema. Histologic examination disclosed typical changes. Gross evidence of periarteritis nodosa, according to Gruber,<sup>37</sup> was lacking in the gallbladder removed at operation and submitted to him for pathologic study, whereas the microscopic changes were classical. In the first case reported in this paper the lesions, though typical, were not recognized because of lack of acquaintance with the manifestations of the disease until some time had elapsed after the microscopic sections were examined. Under the caption of primary vascular nephritis or renal periarteritis nodosa, Keegan<sup>24</sup> describes a case in which a surgically removed kidney showed characteristic and rather early changes found in a more advanced stage in the opposite kidney and elsewhere at the time of death two months later.

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46 Schmorl. Diskussion zu Benda's Vortrag über Aneurysma und Syphilis, Verhandl. d. deutsch. path. Gesellsch. **6** 203, 1903.

47 Von Haun, F. Pathologische-histologische und experimentelle Untersuchungen über Periarteritis nodosa, Virchows Arch. f. path. Anat. **227** 90, 1919-1920.

48 Morawitz, quoted by Gruber (footnote 4).

49 Kopp, G. Ein klinisch diagnostizierter Fall von Periarteritis nodosa, Deutsche med. Wchnschr. **49** 1239, 1923.

50 Weigeldt. Med. Gesellsch. zu Leipzig, Sitzung 8 Jan. 1924, München med. Wchnschr. **71** 218, 1924.

Before leaving the subject of diagnosis, it may be of value to stress Edens' <sup>51</sup> dictum that in an obscure case having the characteristics of a low-grade sepsis which is bacteriologically negative, and which cannot be logically classified as one of the more common conditions, the possibility of periarteritis nodosa should be entertained and a search for nodules in the skin instituted. The more bizarre and protean the manifestations of a case, the more suggestive of periarteritis nodosa does it become.

#### DURATION, COURSE AND PROGNOSIS

The duration of the illness judged by the clinical symptoms varies usually from a few days to several months, averaging about two months. It is important to bear in mind, however, that the lesions judged by the anatomic changes are not infrequently much older than the clinical history indicates, a fact which may account for the stated brief duration of some of the cases reported. The disease on the whole is chronic and progressive, the course being marked by irregular exacerbations and periods of remission. Occasionally, except for loss of weight and strength, the disease remains latent (Klotz' <sup>35</sup> literature), death being due to an independent condition.

It was formerly accepted that periarteritis nodosa was almost invariably fatal. In a study of the forty undoubted cases collected by Klotz <sup>21</sup> in 1917, with the exception of Schmoil's case in which death occurred from a portal thrombosis after an interval of two years, the mortality was 100 per cent. As Klotz pointed out, this rather astounding death rate is to be viewed in the light that only the fatal cases are properly diagnosed and reported. This assumption has been borne out by subsequent experience, for in 1925 the statistics (Gruher <sup>37</sup>) indicated that from 10 to 12 per cent recovered. It is not unlikely, as pointed out by many writers, that lighter cases of the disease which heal without producing any severe clinical symptoms are not infrequent.

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51 Edens, E. Periarteritis nodosa, *Med Klin* 35 1203, 1923

## Book Reviews

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THE SPECIALTIES IN GENERAL PRACTICE By FRANCIS W PALFREY, M D  
Cloth Price, \$6 50 Pp 729 Philadelphia W B Saunders Company,  
1927

This work is a pretentious volume of 729 pages without illustrations but well printed on excellent paper, which is fortunate, as every volume sold probably not only will be read but also will be kept on the purchaser's desk and used. It consists of eleven sections, one on each of the specialties, written in collaboration with the other members of the Faculty of Harvard Medical School. Each chapter aims to present such knowledge as the specialist thinks the general practitioner should possess concerning his field. The point of view is new, and it is surprising to note the difference between this work and the usual quiz compend or outline to help the student cram for examinations. The material here is carefully sorted, and only points of practical value are stressed. Therapy is discussed only in the conditions in which its management by the family physician would be safe and efficient. In all more difficult matters he is advised to consult a specialist. One is pleased, however, to note the number of conditions in which consultation is not suggested, and this work may be of great value in preventing much of the oversteering of the specialties and unnecessary referring of patients to specialists for trivial causes.

In general the selection of material has been excellent, although the section on dermatology treats of ills which are beyond the ken of the average physician, and such matters as lupus of the larynx or Tay's choroiditis seem rather deep for the family doctor. Also, one wonders why such an important field as neurology was entirely omitted, especially in view of the excellent section on psychiatry.

In such a volume two objects must be sought. First, to rule out all controversial material and give only facts, and second, to give only standard methods of therapy and not allow personal opinions or hobbies to find their way in. I am afraid that numerous sins against both these rules have been committed. Surely the management of normal labor by the repeated hypodermic administration of morphine and magnesium sulphate, followed by ether administered by rectum is a hobby and not a standard method (p 311), also the advocacy of the extended thigh. Would all obstetricians agree that a high leukocyte count is of good prognostic value in puerperal sepsis (p 318)? It is difficult to believe that the gynecologist seriously advocates the creation of vesicovaginal fistula to cure chronic cystitis or that such fistulas always heal spontaneously (p 212).

In the section on surgery one finds instructions to use Lugol's solution in cases of toxic goiter (p 677) and to operate at once in any case of appendicitis (p 693), two debatable points to say the least. Finally, it is the unanimous opinion of specialists that if one defers the operation of cleft palate until the child is 2 or 3 years old, as advised here, normal voice is seldom attained. Likewise it is not true that cleft palate does not interfere with nursing (p 663).

Since this review is for an American Medical Association publication, one must comment on the choice of drugs. Will witch hazel cure milk leg, cologne water, cracked breasts, or flaxseed poultices, breast abscesses?

However, these criticisms should not detract from the importance of a valuable book. I anticipate many editions and hope to see a real standard arrived at.

A STATISTICAL SURVEY OF 3,000 AUTOPSIES. By WILLIAM OPHULS, M.D., Stanford University, California. Price, \$2.50. Pp. 370. Palo Alto, Calif. Stanford Univ. Press, 1927.

This monograph is number 3 in the medical series of the Stanford University publications. It is a study based on the results of 3,000 postmortem examinations performed during the years from 1900 to 1923 by Dr. Ophuls and his associates at the Lane and San Francisco Hospitals at San Francisco. In such autopsies gross and microscopic examinations were made of the viscera as a routine. Bacteriologic examinations were made only in cases in which this seemed to be indicated by the nature of the case. A careful and detailed analysis of these 3,000 cases is presented. This is done chiefly by means of charts, of which there are about sixteen, as well as by numerous short tables. The diseases and lesions are classified and named according to the first edition of the "Standard Nomenclature of Diseases and Pathological Conditions, Injuries and Poisonings" issued by the United States Department of Commerce, Bureau of Census, 1920. In the analysis comparisons have been drawn freely between his data and those of other institutions, especially those of life insurance companies.

Dr. Ophuls deserves credit for this painstaking analysis, for it is based on data obtained at the autopsy table and therefore should be much more reliable than masses of data of this sort presented purely from the clinical standpoint.

Attention may be called to a number of interesting points. The fact is brought out that careful search revealed anatomic evidence of acquired syphilis in 95 per cent of all cases (11 per cent of adults). In the majority of the cases, these changes appeared in the aorta.

Under the caption "Infectious Diseases," it is noted that the most numerous deaths were those from diphtheria (15 per cent of all cases). This reveals what still remains to be done in the control of a disease about which apparently so much is known, yet physicians appear to be helpless so far as applying that knowledge in a way that rapidly reduces the mortality is concerned. The work is unique, too, because of the large number of cases of certain rare infections reported, for example, coccidioidal granuloma (seven cases). Nowhere but in California could such a large series of cases of this disease be encountered.

This monograph should be of real service to both pathologists and clinicians, not only in connection with an analysis of their own work, but also from the point of view of comparing the occurrence of various lesions and diseases in different parts of the country.

Mention should be made of the fact that during the past twenty years Dr. Ophuls has made many contributions to the literature, and he has based his intensive studies on the material that is here analyzed. In this connection, one may refer to his work on nephritis and arteriosclerosis.

STUDIES ON ACIDOSIS. By DAUTREBANDE, LABBE and NEPVEUX, and PETREN. Transactions of the French Congress of Medicine, 18th Session, 1925.

In the first part of this exhaustive report, Dautrebande discusses fully the modern conception of acidosis as developed by the American, English and Danish physiologists and biochemists (Van Slyke, Y. Henderson, Haldane,

Barcroft, Hasselbach and others), and includes an explanation of the physiologic mechanism by which acid-base equilibrium is maintained

In the second part of the paper, contributed by Labbe and Nepveux, methods for the determination of acid-base equilibrium, both direct and functional, are given and compared from the standpoints of ease of manipulation and of relative value

The third contribution, by Petren, deals with the pathologic physiology of acid-base equilibrium, and in it are discussed the causes of the acidoses found in emphysema, pulmonary tuberculosis, bronchial asthma, bronchial pneumonia, pneumothorax, morphine administration, diabetes, nephritis, enteritis, cyclic vomiting of children, pregnancy, pernicious vomiting of pregnancy, prolonged fasting, anesthesia, lobar pneumonia, shock (traumatic, infectious and anaphylactic) peptic ulcer, various circulatory disturbances and other less important conditions. The literature of acidosis is reviewed in relation to each of the conditions mentioned

The report as a whole is an excellent exposition of the modern view of acidosis and a thorough review of the literature on the subject. The author is frank in giving credit to contributors on this subject when credit is due. The bibliography refers to more than 300 articles.

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It occurred on three occasions in a diabetic boy (P S ) 4 years old, following indiscretions of diet. He also had a *Giardia* infection. This boy had a twin brother and a younger sister (3 years) also infected with *Giardia*, but who are developing normally for their age and give no history of intermittent diarrhea. The parents and one other child (18 months) are noninfected.

Diarrhea occurred once in a girl with tuberculous adenitis, but she had no *Giardia* infection.

It was present intermittently in a boy (P S ) from the time he was 11 months of age until he was almost 4½ years old. He entered the hospital on account of an enlarged abdomen, and following a thorough study of the case a diagnosis of celiac disease was made. The boy was placed on a high protein diet and did very well in the hospital. His abdomen on his first entrance to the hospital, June 25, 1923, measured 25 inches in circumference, and 26½ inches on his last discharge, Jan 3, 1926. He had grown from 33½ to 37 inches in height, and from 28¼ to 38 pounds (12.8 to 17.2 Kg) in weight. The diarrhea in this case can be accounted for on the basis of the celiac disease, and when improvement began following the feeding of a proper diet, the diarrhea grew milder and recurred less frequently, and it was entirely absent during the last two and one-half months.

In this small group of cases, it is seen that diarrhea may occur in a decided minority of the children infected with *Giardia*, and as a matter of fact, it may occur almost as frequently in noninfected children. When the diarrhea was significant enough to be made the chief complaint on entry, it was due to an improper diet.

Among children, *Giardia* was said to cause only diarrhea but in adults there is not the same agreement among physicians. For example, Galli-Valerio<sup>29</sup> and others believe that diarrhea alternates with constipation when *Giardia* infections occur in man, but Smithies<sup>30</sup> reports diarrhea only and the complete absence of constipation as a symptom in all his cases, while Hollander<sup>19</sup> states that three of his patients were always constipated and none of them had a history of diarrhea.

When this question of the relation of giardiasis to diarrhea among adults is studied, it is interesting to note that in the examination of the stools of 3,187 American soldiers, of whom 269 stated that they had diarrhea at the time the stools were taken and 2,918 stated that they did not have it, that *Giardia* was present in 63 per cent of the group with diarrhea and 54 per cent in the group without diarrhea. Again

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29 Galli-Valerio, B. La Lambliase, Rev. med. de la Suisse Rom. 44:1 (Jan) 1924.

30 Smithies, F. Protoziasis Occurring in Temperature Zone Residents. A Study of 265 Instances with a Discussion of the Associated Digestive Malfunction, Am. J. Trop. Med. 6:1 (Jan) 1926.

only seventy-eight cases gave a history of diarrhea or dysentery, while 6,042 did not, and of these *Giardia* occurred in 51 per cent of the group with a positive history of diarrhea and dysentery and 56 per cent of the group with a negative history (derived from tables 21 and 22, Boeck and Stiles<sup>3</sup>)

This almost identical rate of infection among persons with diarrhea or a history of it, as compared with those who did not have it when the stool was submitted or who had no history of diarrhea or dysentery, appears very significant. It would tend to show that statistically at least, *Giardia* has no relation to diarrhea in adults. The fact that 6,042 men made a declaration of having no history of diarrhea or dysentery as compared with only seventy-eight who did (while the rate of infection among them was practically identical) certainly would tend to show that by and large diarrhea is relatively infrequent in *Giardia* infection. I arrive, therefore, at the same conclusion regarding the relation of giardiasis to diarrhea among adults as I did for children in the foregoing, that statistically, at least, there is little evidence to support the view that *Giardia* causes diarrhea.

How then can I account for the widespread belief among physicians that *Giardia* causes diarrhea in man? The belief has come about as a result of three main factors.

In the first place, as a result of some treatment the physician stopped the diarrhea and thought also he did away with the infection. The accumulation of hundreds of such cases of reported "cures" had the effect of actually convincing some physicians that the flagellates cause the diarrhea. Such evidence, however, is for the most part worthless, for it has been stated above that with the probable exception of a few well controlled cases the "cure" was only apparent since it caused only a cessation of the diarrhea and not an eradication of the infection as subsequent fecal examinations showed.

In the second place, the physician sees patients who are ill and who as a group represent selected cases, in that most of them are either having diarrhea or give a history of intermittent attacks, and when *Giardia* is found in their stools, the etiology of the diarrhea is attributed to this protozoan—no further evidence is often sought. Again, such evidence is entirely biased and tells but a small part of the story for it should be remembered that the well persons harboring *Giardia*, but in whom diarrhea does not occur, do not come into the hands of the physician (as they do in a protozoan survey) and so their infection remains undiscovered. This explains then why most of the physician's patients with *Giardia* infections have diarrhea, or a history of it, and also why in a protozoan survey, more persons have no diarrhea or history of it than persons who do, while the rate of the infection among both is the same.

In the third place, the belief that *Giardia* causes diarrhea is also based on certain data derived from animal inoculation experiments, and on observations of lesions found at postmortem in the human intestine. This evidence has true scientific value, and it is worth while to pass critical judgment on it.

Kantor<sup>17</sup> states that "the facts pointing most strongly to the pathogenic rôle of *Lamblia* (*Giardia*) have been well presented by Fantham and Porter, who found postmortem destructive changes in the intestinal epithelial cells, and by Fairise and Jannin, as well as by Kofoed and Christiansen, who found the parasite embedded in the deeper layers of the intestinal mucosa."

The evidence from these three sources will now be reviewed and also some additional data not mentioned by Kantor.

Fantham and Porter<sup>10</sup> state that they succeeded in infecting kittens and mice, supposedly free of any other species of *Giardia* peculiar to themselves, with *Giardia* from man. Two out of the nine mice were resistant to infection. Some of them developed diarrhea and some did not. Four out of the seven mice infected died. Postmortem observations were as follows: (a) erosion of mucous membrane and falling off of whole villi, (b) small duodenal ulcers, (c) desquamated epithelial cells in the lumen bearing *Giardia* on them, and (d) a condition of generalized inflammation. They concluded that rats may serve as reservoirs of infection for human beings, and that *Giardia* may be conveyed to man from rodents.

It must be obvious to any one who has read the foregoing article of Fantham and Porter that their results do not permit of the conclusions that they draw, but on the contrary, their work suggests that since *Giardia lamblia* infections are so fatal to mice, it would seem most probable that these rodents are not reservoirs at all. Furthermore, they offer no proof that man may get his infection from mice and as stated above, Moritz and Holz<sup>12</sup> were unable to infect man with the cysts of *Giardia* found in mice.

Deschiens'<sup>31</sup> results were similar to those of Fantham and Porter, but considerable skepticism now exists regarding these experimental studies since the work of Simon,<sup>11</sup> who was unable to infect either culture or wild rats with *Giardia lamblia*, and none of the rats "showed any signs of sickness, viz, diarrhea." He concluded that human giardiasis was of human origin.

Kofoed and Christiansen<sup>4</sup> reported the observation of *Giardia muris* in the field mouse deep down in the crypts of Lieberkuhn, and that these organisms caused "chronic enteritis, especially in young hosts, with

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31 Deschiens, R. Les enterites à *Giardia* (*Lamblia*), travail Lab Parasit Faculte de Med Paris, Imprimerie Jehlen, 1921

inflation and yellowish color of intestine" Boeck<sup>32</sup> stated that in the meadow mouse, *Giardia microti* causes a chronic enteritis accompanied by the erosion of the mucous lining, and the disintegration and falling away of epithelial cells and even of whole villi into the lumen, but there is no gaseous distention. These results are similar to those of Fantham and Porter<sup>10</sup> in their experimental work cited above.

My study of the microscopic sections which provided the basis for the foregoing statement regarding the signs of enteritis caused by *Giardia microti* in meadow mice has demonstrated that the evidence cannot be attributed to *Giardia* alone, if at all. New material more carefully fixed immediately after death and then stained shows no evidence whatsoever of enteritis with disintegration and falling away of villi, or any desquamation of epithelial cells beyond what one finds generally. Even the cells on which a flagellate has fastened itself shows no signs of irritation or damage and the secretory activity of the goblet cells is not interfered with (accompanying figure). A small amount of mucus is present in the crypts, but there is no hypersecretion on the part of the epithelium as a result of irritation, such as occurs in amebic colitis. It seems likely, therefore, that my previous observation and those of Fantham and Porter and others can be attributed to poor material, too much manipulation of the tissue, and to postmortem phenomena.

There is so far as I know only the evidence reported by Fairise and Jannin<sup>33</sup> that is based on observations on the human intestine at necropsy. These investigators had a patient who suffered from severe diarrhea for ten months and *Giardia* was found in the stools. They believed that they had satisfactorily ruled out the possibility of intestinal tuberculosis, bacillary and amebic dysentery and worm infection. The case came to necropsy, and a large mamelonated, cauliflower-like growth with ulcerations was found in the cecum, as well as ulcers in the transverse colon and the lower ileum, but no damage was seen in the rest of the small intestine. Microscopic examination of fixed and stained tissues revealed ulcers with necrotic purulent edges, filled with cellular debris. Marked leukocytic infiltration was present, and both motile and encysted forms of *Giardia* were found deep in the mucosa, submucosa and in the muscularis coat whenever an ulcer extended that far.

This evidence is the strongest of any known that tends to incriminate *Giardia* as a true pathogenic parasite of man, but unfortunately the case is obviously not crystal clear. The condition of the duodenum and jejunum, the regular habitat of *Giardia*, was reported normal, while the

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<sup>32</sup> Boeck, W. C. Mitosis in *Giardia Microti*, Univ. Calif. Pub. Zool. **18** 1, 1917.

<sup>33</sup> Fairise, C., and Jannin, L. Dysenterie chronique a *Lamblia*, etude parasitologique et anatomo-pathologique, Arch. d. med. exper. et d'anat.-path. **25** 525, 1913.

flagellates were found in gross lesions outside their normal abode, i. e., the lower ileum, cecum and transverse colon. An explanation is offered here, that the results of examination suggest that this was probably a case of chronic ulcerative colitis, complicated by a cecal ulcerated neoplasm, and that the diarrhea was due directly to these conditions. A marked diarrhea such as this patient had, resulting from irritation and increased peristalsis, was of itself sufficient to bring down the flagellates from the duodenum and some of them became entrapped in the ulcers and crypts of the neoplasm. Here, some of these underwent encystment, they do this normally in the lower ileum and colon. If *Giardia* were solely responsible for the diarrhea and the pathologic findings, it seems strange that no lesions were found in the duodenum and jejunum where the flagellates live in greatest numbers.

In this connection, it may be mentioned that Smithies<sup>30</sup> regards *Giardia* as a secondary invader of ulcers whenever they are present, and that the lesion may be kept open by the flagellates.

Galli-Valeio<sup>29</sup> reported the presence of *Giardia* in a rat and a rabbit dying from diarrhea, but here again since other etiologic factors were not eliminated, there is no scientific evidence for incriminating *Giardia*, for as in the case of chronic enteritis in field mice attributed to *Giardia muris* by Kofoid and Christiansen,<sup>1</sup> mere appearances are not sufficient by themselves in the absence of reliable pathologic evidence.

Porter,<sup>34</sup> in South Africa, reported the occurrence of *Giardia* in samples of water "used previously by the parents of native children at the Johannesburg Hospital in preparing food for the infants, identical with those present in the motions of the children." When the food of clean rats was mixed with this contaminated water, the animals contracted diarrhea, passing large numbers of parasites in the feces.

The theories for the production of the diarrhea are manifold, and all as yet without any proof. It is asserted, for example, that the *Giardia*, because of their numbers, irritate the intestinal epithelium and this results in a "catarrhal condition of the mucosa" and often diarrhea if the secretion of mucus is very great. Wenyon<sup>35</sup> stated that "the occurrence of repeated attacks of diarrhea with a certain degree of abdominal uneasiness preceding the attacks and the passage of such extraordinary numbers of flagellates, especially in the mucus, leads me to suspect that sometimes, at any rate, *Giardia intestinalis* may produce sufficient irritation of the small intestine to justify us in regarding it as pathogenic." But, to date, I know of no pathologic evidence gained from a study of stained sections of the intestine that lends any proof to this idea, and

34 Porter, A. A Survey of the Intestinal Entozoa. Observed Among Natives in Johannesburg, Memoirs South African Instit. M. Research, no 11, 1919, p. 39.

35 Wenyon, C. M. Observations on the Intestinal Protozoa, Their Diagnosis and Pathogenicity, Lancet 2 1173, 1915.

clinical evidence alone is not sufficient since other factors alone or associated with the presence of the *Giardia* might produce the irritation and diarrhea. The same mucoid type of diarrhea, minus the flagellates, may be seen at times in uninfected persons.

Smithies<sup>30</sup> offers as an explanation of the diarrhea the suggestion that the diarrhea represents a toxic manifestation dependent on the absorption of poisonous amines which have resulted from a splitting of dead protozoa and bacteria, or of food proteins by the action of bacteria, which he believes are unusually abundant in stools that contain protozoa. In support of this idea, he states that the administration of substances that "sharply decrease the degree of bacterial activity in the intestine and yet have little or no effect upon protozoa" changes the physical characteristics of the stool and the "diarrhea is ameliorated or ceases."

It will be difficult to obtain proof for or against this theory until more is known of the constitution of the protozoan body and its fate after death. The supporting evidence cited by Smithies hardly touches the case, however, for it would be only in cases of achylia gastrica for the most part that a rich bacterial flora would occur in the duodenum, jejunum and upper ileum (the zone of rapid absorption and the habitat of the flagellates) and there cause the protein splitting of the dead *Giardia* and bacteria, for normally the bacteria are most prevalent in the large intestine beyond the habitat of *Giardia*. Again, if certain drugs affect the bacterial activity, and at the same time not the protozoa, so as to cause a disappearance of the diarrhea, it seems likely that in most cases the effect of the drug was not manifested until it reached the large intestine, where the bacteria predominated, and we could as justifiably draw the conclusion that the diarrhea was probably of bacterial origin from fermentative and putrefactive processes acting on material in the colon, as to attribute it to the protozoa living high up in the small intestine. Smithies<sup>30</sup> stated that it is not possible to attribute the diarrhea to disturbed gastric secretory function, for in one third of his cases of *Giardia* infection the gastric values were normal.

A general criticism that seems to apply to all claims that *Giardia* is pathogenic and causes diarrhea, symptoms of abdominal pain, tenderness, nausea and vomiting is that, clinically, no characteristic symptomatic onset has been described that would suggest the beginning of the infection or the pathologic process, should the latter not coincide with the date of infection. The diarrhea due to improper feeding of infants, or to dysentery bacilli in children and adults, has a typical onset as to time, signs and symptoms. In infections of *Giardia*, however, the time of the acquisition of the infection is unknown to the host since he is unaware of any characteristic symptoms.

Let us now consider the relationship of *Giardia* infections to disease of the gallbladder.

## GALLBLADDER DISEASE

Disease of the gallbladder is often dependent on infections of the gastro-intestinal tract. This fact has been demonstrated by the experimental studies of Grieg,<sup>36</sup> Nichols,<sup>37</sup> Parker and Franke,<sup>38</sup> and Meyer, Nelson and Feusier,<sup>39</sup> for infections of typhoid, paratyphoid A and B, dysentery and cholera bacilli. Recently, the review of Soper<sup>40</sup> shows that this relationship also extends to other infections as well. In 411 cases of gallbladder disease, it was found that in 121 cases there was a history of puerperal infection while the origin was obscure or unknown in 120 other cases, but a definite relation to gastro-intestinal infections existed in the remaining 170 cases. Twenty-two per cent gave a history of typhoid, 10 per cent, dysentery, 17.6 per cent purulent proctosigmoiditis, 7 per cent, chronic ulcerative colitis, 20 per cent, chronic catarrhal colitis, 7 per cent, colonic diverticulitis, and 15 per cent had gastritis anacida.

Many physicians, especially many of the gastro-enterologists, have come to believe that *Giardia* infections are also related to the causation of gallbladder disease. It is believed that the flagellates may either initiate the disease process in the gallbladder by their migration from the duodenum or that they may play the part of a secondary invader and prolong an already existing cholecystitis of probable bacterial origin.

Smithies<sup>41</sup> reported the presence of viable *Giardia* in the contents of the gallbladder removed at operation from a man with acute symptoms of gallbladder disease. This observation was a most important one and it demonstrated that under certain pathologic conditions, *Giardia* does obtain entrance to the gallbladder and may remain viable in the concentrated bile of this organ.

Subsequently, the belief in the probability of *Giardia* causing cholecystitis grew tremendously as a result of the extensive and common practice of the Meltzer-Lyon method of drainage of the biliary tract.

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36 Grieg, E. D. W. An Investigation on the Occurrence of the Cholera Vibrio in the Biliary Passages, *Indian J. M. Research* **1** 44, 1913-1914, Lesions of the Gallbladder and Biliary Passages in Cholera, *ibid* **2** 28, 1914-1915.

37 Nichols, H. J. Experimental Observations on the Pathogenesis of Gallbladder Infections in Typhoid, Cholera and Dysentery, *J. Exper. Med* **24** 502, 1916.

38 Parker, J. T., and Franke, E. The Fate of Typhoid Bacilli Injected Intravenously into Normal and Typhoid Immune Animals, *J. M. Research* **39** 301 (Jan.) 1919.

39 Meyer, K. F., Nelson, N. M., and Feusier, M. L. A Comparative Study of the Infections Produced by Intravenous Injections of Typhoid, Paratyphoid A and B Bacilli in Normal and Immunized Rabbits, *J. Infect. Dis* **28** 408 (May-June) 1921.

40 Soper, H. W. Relationship Between Disease of the Gallbladder and Infection in the Gastro-Intestinal Tract, *Ann. Clin. Med* **4** 422 (Nov.) 1925.

41 Smithies, F. *Tr. Am. Gastro-Enterological A.*, 1925.

with a duodenal tube and the administration of magnesium sulphate *Giardia* was occasionally found by this means in the fasting contents of the duodenum, and in the B fraction (supposedly coming from only the gallbladder) What seemed more important was the finding of the flagellates at times in the B fraction when they had not been found in the duodenal contents before the administration of the magnesium sulphate Such observations were recorded by Knighton,<sup>42</sup> Hollander,<sup>43</sup> Labbe, Nepveux and Gavrilá,<sup>43</sup> Lyon and Swalm<sup>44</sup> and others These observations were interpreted to mean (1) that *Giardia* may ascend the common and cystic ducts and reach the gallbladder, and (2) that they might be present in the gallbladder while absent from the duodenum and thus be in a position in which they could bring about reinfection of the duodenum, should the latter be free following treatment

It will be observed that with the exception of the case cited by Smithies in which *Giardia* was actually found in the gallbladder removed at operation, the only evidence suggesting that this flagellate may live in this organ is its occurrence in the B fraction of the bile, for *Giardia* has not been observed in any other gallbladders removed at operation, even in cases in which the flagellates were known to be present in the duodenum (Simon,<sup>18</sup> Silverman, in Simon,<sup>18</sup> and Lyon and Swalm<sup>44</sup>)

Evidence, however, that is based on the observation of *Giardia* in the B fraction of the bile during biliary drainage is not dependable It is not dependable because the source of the B bile cannot be attributed to the gallbladder alone for it may come from the liver directly

Bile in the B fraction in the Meltzer-Lyon test is recognized by its darker color as compared to that in the common hepatic duct and flows as a continuous stream for some time after magnesium sulphate has been given Bile of the same color, however, has been obtained in cases in which the gallbladder was prevented from emptying its contents following the administration of magnesium sulphate because of a blocking of the cystic duct by a stone<sup>45</sup> or even in the absence of the gallbladder when hepatitis probably was present, as reported by Dunn and Connell<sup>46</sup> and others Likewise, when dyes were injected into the gallbladder,

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42 Knighton, J E *Lambia Intestinalis*, with Report of Cases, South M J **15** 457, 1922

43 Labbe, M, Nepveux, F, and Gavrilá *Lambiasis of the Gallbladder*, Bull Soc med d hôp de Paris **49** 1505, 1925

44 Lyon, B B V, and Swalm, W A *Giardiasis Its Frequency, Recognition, Treatment and Certain Clinical Factors*, Am J M Sc **170** 348 (Sept) 1925

45 Einhorn, M *Action of Various Salts and Other Substances on the Liver After Their Introduction into the Duodenum*, New York M J **114** 262 (Sept 7) 1921

46 Dunn, A D, and Connell, K *A Report of a Case of Hepatoduodenostomy*, J A M A **77** 1093 (Oct 1) 1921

B bile was obtained, but none of the dye was present in it <sup>47</sup> The color of bile alone, therefore, does not indicate the source of the bile, and because of this fact it is important to consider the character of the sediment also in ascertaining where the bile comes from Jones,<sup>48</sup> however, obtained bile that appeared like B bile, and was identical with it as determined by spectroscopy, in a patient in whom the gallbladder previously had been removed

A number of investigators, Crohn, Reiss and Radin,<sup>49</sup> Johnson,<sup>50</sup> Harer, Hargis and Van Meter <sup>51</sup> and others did not obtain a contraction and emptying of the gallbladder following the administration of magnesium sulphate Silverman and Menville,<sup>52</sup> Sosman, Whitaker and Edson <sup>53</sup> and Whitaker,<sup>54</sup> however, by means of cholecystography have shown that the gallbladder shadow becomes smaller after magnesium sulphate has been given intraduodenally, and they have interpreted this to be due to the contraction of the gallbladder The gallbladder does not empty itself completely and this is in accordance with the work of Johnson,<sup>50</sup> who found that one could repeat the Meltzer-Lyon test four times within forty to sixty minutes and obtain B bile each time

The more recent investigations of Boyden <sup>55</sup> and Whitaker and Boyden <sup>56</sup> have demonstrated that although the gallbladder does empty partly after administering magnesium sulphate, a much better result with complete emptying of the gallbladder brought about by rhythmic contractions of its musculature is obtained following a lipid meal of egg yolk and cream

47 Crohn, B B , Reiss, J , and Radin, M J Experiences with the Lyon-Meltzer Method for the Diagnosis of Gallbladder Disease, *J A M A* **76** 1567 (June 4) 1921 Diamond, J S An Experimental Study of the Meltzer-Lyon Test, with Comment on the Physiology of the Gallbladder and Sphincter Vatri, *Am J M Sc* **166** 894 (Dec ) 1923

48 Jones, C M The Rational Use of Duodenal Drainage, *Arch Int Med* **34** 60 (July) 1924

49 Crohn, Reiss and Radin (footnote 47, first reference)

50 Johnson, W O The Function of the Gallbladder, with Special Relation to the Meltzer-Lyon Test, *Surg Gynec Obst* **34** 177, 1922

51 Harer, W B , Hargis, E H, and Van Meter, V C Studies of the Function of the Gallbladder, *Surg Gynec Obst* **34** 307 (March) 1922

52 Silverman, D N, and Menville, L J Observations of Visualized Gallbladder by the Graham Method, with Reference to the Effect of Nonsurgical Biliary Drainage Preliminary Report, *J A M A* **84**.416 (Feb 7) 1925

53 Sosman, W C , Whitaker, L R, and Edson, P J Clinical and Experimental Cholecystography, *Am J Roengenol* **14** 495-503 (Dec ) 1925

54 Whitaker, L R Experiences with Cholecystography, *J A M A* **86** 239 (Jan 26) 1926

55 Boyden, E A The Effect of Natural Foods on the Distention of the Gallbladder, with a Note on the Change in Pattern of the Mucosa as It Passes from Distention to Collapse, *Anat Rec* **30** 333, 1925, Observations on the Physiology of the Gallbladder, abstr , *Am A Anat Rec* **32** 202 (March) 1926

56 Whitaker, L R, and Boyden, E A Observations on the Function of the Gallbladder, *Am J Physiol* **76** 199 (March) 1926

As a result of these studies, we may conclude that the gallbladder does contract following magnesium sulphate and that B bile does come from this organ, but it should be remembered that bile of the same color and constitution may be obtained in some cases of cholelithiasis with cholecystitis, or in persons who have no gallbladder. It is presumed that in these cases, the dark bile comes directly from the liver. Since the source of the B bile cannot be attributed to the gallbladder alone with certainty in all cases, it would appear to be illogical to assume that presence of *Giardia* in this particular fraction of the bile constitutes proof that they have come from the gallbladder.

How then is the occurrence of *Giardia* in the darker bile to be explained when it was absent in the duodenal fasting contents? Hollander<sup>10</sup> often found that following the injection of hypertonic salt solutions the flagellates occurred in floculi from the duodenal crypts when none had been seen in specimens of the duodenal fluids. This may be explained, I believe, by the action of the salt solution on the intestinal mucosa. Magnesium sulphate as employed in the Meltzer-Lyon test is an irritant to the intestinal mucosa and causes an increased secretion of mucus, and because of its hypertonicity it also results in an extraction of water from the same tissues. This action of the salt results in an increased flow of fluid out of the glandular crypts carrying the flagellates with it into the lumen of the duodenum.

I have also observed that a continuous flow of fluid (from 5 to 15 cc) lighter in color than that previously dropping into the flask occurred a few minutes after the administration of from 25 to 30 cc of warm water through the duodenal tube. This lighter colored yellow fluid also contained fewer flagellates and when the bile resumed its deeper, golden yellow again the flagellates were present in increased numbers also. No continuous flow of dark bile (B) was obtained. This result was explained by supposing that some of the warm water was regurgitated as a result of a wave of reverse peristalsis in the duodenum and when the water reached the region of the tip of the duodenal tube, the duodenal contents became diluted, resulting in a lighter colored fluid and fewer flagellates per unit volume of contents. The flow became continuous because of the increase in pressure and larger amount of fluid in the particular area brought about by the wave of peristalsis. This explanation is in accord with Johnson's<sup>50</sup> observations that the sphincter of Oddi failed to respond to stimulation with water.

More observations, however, are necessary before adequate proof can be had for this explanation, but it must always be considered probable that failure to find *Giardia* in the duodenal fasting contents and only in the B fraction can be reasonably explained either as Hollander has done, by showing that the hypertonic salts apparently cause the *Giardia* to come out of the crypts as explained above, or by the carriage of the flagellates from a lower duodenal or jejunal segment upward to

the area of the duodenal tip, as a result of a reverse wave of peristalsis, and there the organisms mix with the outflowing B bile

We may conclude, therefore, that the evidence furnished by duodenal drainage is not reliable proof that *Giardia* normally ascends the common and cystic ducts to live in the gallbladder. The only evidence that is conclusive is the actual presence of these flagellates in the gallbladder, but the single case observed by Smithies is hardly sufficient, for even in this instance it is not clear that *Giardia* caused any damage. Its entrance in this one case may have been gained as a result of a dilated exit of the common duct in the papilla of Vater brought about by an antecedent pathologic condition.

The presence or absence of a preexisting pathologic process must be determined in all cases, for on the observations depends the solution of the question whether *Giardia* by itself may cause chronic gallbladder disease or only be of the nature of a secondary invader.

Lyon and Swalm<sup>44</sup> pointed out that among 798 persons, in 80 per cent of whom gall tract disease was recognizable, *Giardia* occurred in only twenty cases, an almost insignificant proportion. They and others, however, did not obtain *Giardia* from gallbladders removed at operation as reported by Smithies in one case.

If the migration of *Giardia* to the gallbladder were not preceded but were followed by pathologic changes, then it would appear probable that the initial damage could be attributed to the flagellates, the picture later on becoming complicated by bacterial infection as well. This view, however, does not seem probable on the basis of the data available for the following reasons: (1) because gallbladder disease is much less frequent in children than in adults, although a larger proportion of children are actually infected than is the case with adults, (2) many, if not most of the cases of chronic cholecystitis are of bacterial origin, and (3) in gallbladder disease as well as in diarrhea, by far more persons are infected with *Giardia* and have no symptoms and therefore are not seen by the physician than there are those who do. This may be seen by observing the greater rate of infection for *Giardia* in children and adults (table 1) as compared to the incidence of gallbladder disease that is attributed to or associated with an infection with *Giardia*. In Lyon and Swalm's<sup>44</sup> series, the latter incidence was around 3 per cent (80 per cent of 798 cases showed findings of cholecystitis, of which twenty had *Giardia*).

It is likely from the present data that *Giardia* does not ascend the common and cystic ducts and reach the gallbladder except in rare instances, but is confined normally to the duodenum and upper jejunum. Its entrance into the biliary passages and then the gallbladder, as was found in the case cited by Smithies, would appear probably dependent

on antecedent disease involving the sphincter of Oddi in the papilla of Vater, so as to cause a temporary or permanent dilatation of the end of the common duct, and thus allow the migration of the flagellates up this passage and the cystic duct into the gallbladder

The occurrence of such lesions must be rare, however, in acute chronic gallbladder disease because the removal of the gallbladder is generally followed by a complete and permanent disappearance of the symptoms, even in the few cases noted thus far that have shown duodenal infection with *Giardia* previous to and after the operation. Cholecystectomy does not rid a person of his intestinal infection with *Giardia* and this is what might be expected since the duodenal environment in which the protozoa live is not altered physiologically by the absence of the gallbladder. This was well illustrated in the case of the small diabetic boy, referred to in a previous portion of this article, who developed cholecystitis when he was 3½ years of age.

The history of this 4 year old boy's illness is very interesting in that it shows how early gallbladder disease may occur in the life of a diabetic child, and it permits of speculation as to the rôle played by *Giardia* in the production of the cholecystitis.

This boy had an acute attack of diarrhea following the eating of watermelon at the age of 15 months and three weeks later developed diabetes mellitus. He entered the Infant's Hospital, July 31, 1923, and since that time he has spent most of his life in the Infants' and Children's Hospitals. Since September, 1925, he has been at the Boston City Hospital (Thorndike Memorial Laboratory). While in these hospitals he was not troubled with diarrhea except on one occasion in the Infants' Hospital. He ran a swinging temperature (except for a period of eleven days) from 97 to 98 in the morning to 99 to 100 in the afternoon with periodic elevations above 100 to 102, it once reached 106, when the attack of diarrhea occurred. His white count was always elevated from 16,000 to 18,000. He was negative for both Shick and tuberculin tests. Acute diarrhea for a day occurred once more in August, 1925, just before his last entrance to the Children's Hospital, probably as a result of breaking away from his prescribed diabetic diet.

In the Boston City Hospital, his temperature behaved in the same way as before, and his white count was always elevated and as high as 29,500. He became definitely jaundiced, Oct 25, 1925, and tender in the upper right quadrant. Subsequently gallbladder roentgenograms were made on three occasions, the dye being given by mouth once and intravenously twice, and no shadow appeared. A cholecystectomy was done. The microscopic examination revealed evidence of chronic cholecystitis. Following the operation the child's temperature ran along normally for the first time, likewise, his white count became normal, and his diabetic condition, much improved. Examination of the gallbladder, microscopically, failed to show any *Giardia* present. Fecal examinations revealed the presence of the cysts, however, so the operation did not clear up the flagellate infection. There have been no attacks of diarrhea during his entire stay in the Boston City Hospital thus far (ten months). The *Giardia* infection has persisted since the operation, but the swinging temperature, elevated white count, and symptoms of pain, tenderness and jaundice disappeared completely, and have not recurred.

Some clinicians would probably have attributed the cholecystitis in this diabetic boy to the *Giardia* infection, merely because it was a complicating feature, but this interpretation does not seem warranted in view

of the absence of the flagellates in the removed gallbladder, the complete disappearance of symptoms following the operation, and the persistence of the *Giardia* infection in the duodenum. It seems more probable that the cholecystitis may possibly have originated from a duodenitis of bacterial origin at about the time the patient developed diabetes and that an extension of the inflammatory process or infection to include the gallbladder occurred. In this organ, the disease process developed and persisted even after the duodenitis had subsided. Whether or not *Giardia* may have had anything to do with the duodenitis and the extension of the infection is a matter of speculation, but to me it appears most unlikely since gallbladder disease is so uncommon in children as compared to the incidence of *Giardia* infection, and since the boy became symptomless after the operation.

The boy's twin brother and a 3 year old sister are also infected with *Giardia*. To date, however, there is no history of a sharply defined onset characterized by an acute gastric upset followed by irregular temperature, leukocytosis and the development of diabetes mellitus such as their brother had, in fact, the children have enjoyed normal development thus far and have led no one to suspect that they too had a *Giardia* infection. These cases appear to offer "control" evidence that *Giardia* infections are not etiologically related to gallbladder disease.

The duodenum being the normal habitat of *Giardia*, they are located favorably for playing a part in the production of gallbladder disturbances but, if they do, the exact mechanism by which they enter the biliary tract and produce disease has not been discovered, and the present evidence that seeks to convict these protozoa of causing disease of the duodenum and gallbladder is meager, for the most part unscientific and unconvincing. We are in need of controlled evidence based on experimental and pathologic studies before we can definitely state that *Giardia* reaches the gallbladder or other organs sufficiently often (if at all) to be a factor of importance in the etiology of cholecystitis, and whenever it is found there it should be determined whether it is a primary cause of gallbladder disease or only a secondary invader that has gained access to the biliary tract because of antecedent disease involving the papilla of Vater.

#### ARTHRITIS DEFORMANS, NEURESTHENIA, MELANCHOLIA, ETC

Barrow<sup>57</sup> and others have attributed the etiology of arthritis deformans, and various poorly defined and obscure states of ill health, referred to as neurasthenia, melancholia and dyspepsia and characterized by symptoms of nausea, belching of gas, epigastric or generalized abdominal pain and tenderness, loss of "pep" and weight, to *Giardia* (and other intestinal protozoa) whenever this infection is found. No

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<sup>57</sup> Barrow, J. V. A Clinical Study of the Intestinal Protozoa, Based on Seven Hundred and Twenty-Five Cases, *Am J Trop Med* 4:23 (Jan) 1924.

evidence, however, was furnished that is scientific and convincing, but only conjectures of theoretical value were made. At present, therefore, it seems unlikely that *Giardia* is an etiologic factor in the causation of these conditions.

#### SUMMARY

*Giardia* infections occur more often in children than in adults, and the incidence of infection is remarkably high in children from 1 to 7 years of age. The infection appears to be acquired, as a rule, after the first year of life.

*Giardia* is said to cause recurrent diarrhea in children, and diarrhea only or diarrhea alternating with constipation in adults. Diarrhea in young children is more frequent than in older children and adults, but this is due to the fact that most cases are due to improper feeding or to colitis due to dysentery bacilli.

In children and adults as a whole statistical studies indicate that diarrhea does not occur any more frequently in those persons infected with *Giardia* than among noninfected persons.

The belief among physicians that *Giardia* causes diarrhea appears to be due to three factors: (a) numerous reported "cures" are now known to be in most cases without basis of fact, (b) reported cases of diarrhea and "cure" by physicians on a group of selected, sick persons complaining of diarrhea at the time or in the past, such evidence is one-sided for the well persons with *Giardia* infections do not come under the physician's care but are seen and examined in protozoan surveys that by the very nature of things do not include such an exclusive selection of persons, (c) animal inoculation experimentation and the observation on material obtained at necropsy of man infected with *Giardia* are cited as evidence, but a review of the data shows the evidence to be either meager and devoid of proper control measures or open to other and as logical interpretations. They are at best quite inconclusive and demanding of more confirmatory observations.

There appears to be no specific symptomatic onset that characterizes infections of *Giardia* clinically.

If we weigh the evidence at hand, there is little in the way of scientific proof that indicates *Giardia lamblia* itself causes diarrhea in either children or adults, except perhaps in a few obscure and sporadic cases, and as much or more evidence, some of it statistical and some pathologic in character, that indicates that this protozoon does not cause diarrhea. It remains to be proved, however, whether *Giardia* might influence temporarily an existing affection, viz., duodenitis or colitis of bacterial origin which causes or aggravates a diarrhea already present. The evidence pointing to this possibility is totally lacking at present, and all discussions constitute only theoretical speculations.

The finding of viable *Giardia* in the gallbladder following its removal has been reported only in the single case of Smithies. The occurrence

of this flagellate in the B fraction of the bile obtained by the Meltzer-Lyon method of duodenal biliary drainage does not of itself constitute evidence of invasion of the biliary passages, even in cases of chronic cholecystitis. The conclusions reached by various gastro-enterologists that *Giardia* may either cause chronic cholecystitis or secondarily complicate this condition appear to be based on inadequate evidence.

The data at present available indicate that *Giardia* does not initiate any pathologic changes and it is questionable whether it in any way tends to aggravate, prolong or extend preexisting inflammatory conditions of duodenum or gallbladder. This conclusion is deduced from the following facts: (a) *Giardia* up to the present time has been found in only one instance in the gallbladder removed at operation, (b) while in children gallbladder disease is extremely rare, the rate of *Giardia* infection is two or three times as great as in adults in whom cholecystitis is comparatively frequent, (c) *Giardia* infections occur infrequently in persons with disease of the gallbladder, which is, however, frequently a result of gastro-intestinal (bacterial) infection, (d) the symptoms of cholecystitis are cleared up by cholecystectomy, but when associated with *Giardia* this organism may persist after operation, (e) *Giardia* infections may occur in several members of the same family but cholecystitis does not occur in all of them and may never appear.

The rare entrance of *Giardia* to the biliary tract is probably dependent on a lesion in the papilla of Vater involving the sphincter of Oddi and causing a dilatation of the end of the common duct. Such a lesion might allow both bacteria and *Giardia* to ascend to the pancreas, gallbladder and liver and in such instances it seems more probable that any resulting disease condition would be better attributed to the bacterial invasion than to the migration of the protozoa, since the latter produce no demonstrable lesions in the duodenum.

It has not been shown as yet how *Giardia* may produce any disease and the mechanism by which it obtained entrance to the biliary tract in the single case reported still remains obscure. More experimental and pathologic evidence is therefore necessary to determine whether this flagellate may frequently invade the gallbladder or whether it obtains entrance only in the rôle of a secondary invader following an antecedent pathologic condition of the biliary tract.

There is no evidence of scientific value at present to support the theory of Barrow that *Giardia lamblia* is concerned in the etiology of arthritis deformans, certain forms of neurasthenia, melancholia with loss of weight and such symptoms as nausea, vomiting, belching of gas and epigastric pain and tenderness.

## Book Reviews

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DIATETIK DER MAGEN- UND DARMKRANKHEITEN VON I. BOAS, NEBST DIATETIK UND NACHBEHANDLUNG BEI OPERATIONEN AM MAGEN-DARMKANAL VON G. KELLING. Ed 2, enlarged and improved. Leipzig: Georg Thieme, 1926.

The introductory section of this work consists of an excellent statement of the principles of dietetics, with many practical hints as to their application. Simplicity is the keynote, and by the use of a few simple rules and the table given, caloric calculations can be rapidly and accurately made. Throughout the entire work not only the principles but also carefully worked out diet lists are given for almost every manifestation of gastro-intestinal disease. Unfortunately, these diets contain a high percentage of foods not available to the American public. Even their names have no English equivalents, and such lists would need complete revision to have any practical value outside of Germany. Another objection to the lists is the free use of innumerable proprietary foods.

One gets the impression, however, that dietetics is here given a much more important place in therapy than it really deserves. The twelve pages devoted to the dietary management of enteroptosis cannot but make one ask whether enteroptosis is a disease, and, if so, what possible influence diet can have. Again, in the comment on "nervous dyspepsia," one wonders whether the "nerves" are not being neglected while the dyspepsia is being overtreated.

In the latter section of the work dealing with surgical diseases, this fault is still more prominent. The importance of the diet, both before and after operation, is surely overemphasized. The more modern surgical point of view is, "The less interference with the patient's normal diet, the better." The administration of salts plus castor oil as a matter of routine before operation as here recommended cannot be too vigorously condemned. The restriction of food advised for the day before is too great, and the full diet is not restored soon enough to suit most surgeons today.

With the exception of such faults, which are common to all works in this field, the work is a valuable one. The principles underlying the disorders of nutrition are clearly and concisely stated, and an adequate scientific basis is given for the dietary control of these disorders. Finally, the practical means of applying these principles is made available to the general practitioner.

In the broader aspects of metabolism, means other than dietetic regulation are discussed. The water balance, acids and alkali relations, catharsis, enemas, etc., are considered as part of the problem. One of the best chapters in the book is that on extrabuccal nourishment.

PERNICIOUS ANEMIA. By FRANK ALEXANDER EVANS, M.D. Cloth. Pp 170, with bibliography. Baltimore: Williams and Wilkins Company.

It is stated that the object of this book is to draw clinical pictures, reconsider treatment and discuss the more promising lines for study of the etiology of pernicious anemia. Certain considerations of the subject are taken from the field of orthodox discussion. In the chapter on classifications, the lines are more sharply drawn than usual, and there is a clear explanation of the basis on which the division is made.

Authorities are quoted in support of the statement that the number of cases of pernicious anemia is not increasing, and that the condition rarely, if ever, is found in people under 20 years of age. The danger of diagnosing pernicious anemia in the presence of a positive Wassermann reaction without first using thorough antisyphilitic treatment is emphasized. Other points as to incidence considered are the few instances among negroes, its relatively frequent occur-

rence among Americans, Canadians, English, Irish and Scandinavians as compared with the peoples of Southern Europe, its infrequency in tropical Brazil, and the fact that heredity has not been shown to play any part in the matter.

With the exception of etiology, no other phase of this subject is more important for the practitioner than that of diagnosis. In the chapter dealing with this part of the subject, there is a good comparative discussion of the various factors that enter into the possible etiology, diagnosis and pathology of the disease. A comparison of the morphology of the blood as described here, with the descriptions found in the chapter "Clinical Description," leads to more or less the same kind of confusion that one finds in any analysis of the subject.

The subject of pernicious anemia is well presented in this book, which is written for practitioners, but one is inclined to inquire about the principle that should guide the practitioner in the selecting of his library. Monographs dealing with such subjects as pernicious anemia are justified only by some addition to the knowledge of the subject. The number of periodicals and books being published today makes it necessary for the practitioner who would be well informed as to progress in science to be careful of his time and money. It is on this basis that criticism is made of a new book on such a subject as this which makes no addition to what has already been written many times.

PRINCIPLES OF HUMAN PHYSIOLOGY By E. H. STARLING Fourth Edition  
Price, \$8 Pp 1058 Philadelphia Lea and Febiger, 1926

The fourth edition of this excellent textbook differs little from the third which appeared in 1920. By omitting some material belonging more properly to chemistry and anatomy, the volume has been reduced from 1,298 to 1,058 pages.

The sequence in which the various topics are taken up remains unchanged, and it is not always satisfactory from the pedagogic standpoint. The author starts out well enough by a review of the material and the energetic bases of the body which the student should but probably does not know. After treating the most obvious and easily observable phenomena of movement and sensation, he discusses the central nervous system. He has added to the chapter on the cerebrum a brief but satisfactory exposition of Pawlow's work on the conditioned reflexes, but the subject of sleep is not even mentioned. Apparently Professor Starling is one of those who consider sleep unworthy of consideration by physiologists.

After the nervous system the sense organs are discussed, and their physiology receives adequate treatment. From this point on, the arrangement of the material seems to be highly illogical. Digestion and nutrition are considered before circulation and respiration, and it is hardly fair to the student to expect him to comprehend the phenomena of digestion and absorption without a knowledge of the circulation, and to understand metabolism without previous knowledge concerning the blood and respiration. There also seems to be some lack of proportion in the space allotted to the different subjects. Thus the chapter on the eye includes more than 80 pages (none too long, in our opinion), but only 19 pages are devoted to the chapter on the glands of internal secretion. Another shortcoming is the lack of references to the literature which are of value in enabling the curious student to obtain further information on subjects which attract his interest.

As a whole, however, the book is well written and is still one of the best texts on physiology at the present time.

GOITRE AND OTHER DISEASES OF THE THYROID GLAND By ARNOLD JACKSON  
New York Paul B Hoeber, 1926

This work discusses a difficult and complicated subject in a manner that cannot be praised too highly. In all cases the data are reduced to the simplest possible terms, and in this form are of eminently practicable value. The

enormous literature has been sifted carefully and only the positive and proved points made available here for the general practitioner

The first chapter deals with the thyroid gland, its anatomy and development, and concludes with an uncommonly concise statement of its function. This is followed by an equally clear exposition of what is known of its interrelation with other glands of internal secretion.

After the causes of goiter have been given, a classification is made. Here, again, simplicity is attained without sacrifice of truth. The small group of diseases of the thyroid given can be used to express clinical, histologic and physiologic facts with equal success.

The enormous increase of iodine hyperthyroidism since the modern prophylactic iodine medication is thoroughly reviewed. Workable rules are given for the administration of iodine in order to prevent this catastrophe, and comment is made on the whole matter of medical management.

Although the book is written from the surgical standpoint, the basic physiologic principles are not for a moment forgotten. Iodine has practically done away with the necessity for pole ligations. In the section on operative technic there are unfortunately included a number of reproductions of photographs that are poor. The illustrations in most cases are better but not especially clear.

Roentgen-ray treatment is given scant consideration.

THE HUMAN CEREBROSPINAL FLUID. AN INVESTIGATION OF THE MOST RECENT ADVANCES, AS REPORTED BY THE ASSOCIATION OF RESEARCH IN NERVOUS AND MENTAL DISEASE. THE PROCEEDINGS OF THE ASSOCIATION, NEW YORK, DEC 29 AND 30, 1924. EDITORIAL BOARD: CHARLES L. DANA, M.D., THOMAS K. DAVIS, M.D., SMITH ELY JELLIFFE, M.D., HENRY ALSOP RILEY, M.D., FREDERICK TILNEY, M.D., and WALTER TIMME, M.D. Price, \$10. Pp 568, with 77 illustrations. New York: Paul B. Hoeber, 1926.

This is the fourth volume so far published by this active association, which has developed new methods in both organization and publication. There are thirty-nine contributors and, in addition, the volume contains much discussion, chiefly in the form of rigid cross-examination of the writers by the members of the commission to whom the papers are addressed. The following statement by the editorial committee in its preface, in view of the completeness and high quality of the volume, is a conservative estimate: "The committee believes that the volume represents the most up-to-date information on the subject, that it comprises material which up to now has been difficult of accessibility, and that the symposium that it embodies really furnishes the latest investigative results and the best current interpretation of both the physiological and the pathological aspects of the human cerebrospinal fluid."

There are thirty-one separate articles in the seven sections, which have the following titles: 1 The Normal Human Cerebrospinal Fluid, 2 Biological, Chemical and Physical Properties Under Normal and Pathological Conditions, 3 Pressure Studies of the Cerebrospinal Fluid, 4 The Diagnostic Replacement of the Cerebrospinal Fluid by Various Agents, 5 Changes in the Human Cerebrospinal Fluid in Connection with Diseases of the Central Nervous System, 6 The Reaction of the Human Cerebrospinal Fluid in Extranuclear Diseases, and 7 The Treatment of Pathological Conditions Through the Cerebrospinal Fluid.

THE FINER DIAGNOSIS OF ACUTE BRAIN INVOLVEMENTS INCLUSIVE OF SYPHILIS AND BRAIN INJURY. By J. VICTOR HABERMAN, A.B., M.D., S.M.D. (Berlin). Pp 116. New York: Medical Journal and Record.

This is a monograph of 116 pages, nine of which contain bibliography. The acute conditions of the brain are considered from three points of view: the acute infection of the brain and its membranes, the reaction of the individual to brain injury or trauma and the acute vascular incidents in the brain. It

is essentially a compilation. A discussion of the spinal fluid occupies a large part of the text, but perhaps no more than is justifiable. In the chapter on brain injury the author warns against considering any symptoms as purely functional that are not due to organic disturbance of some variety. He does not give any suggestion concerning diagnosis of functional conditions from organic, but, considering the title, he is perhaps right in this stand. The paragraphs on late aneurysm are interesting though no allowance is made for the possibility of coincidence. This is a useful monograph for the student and general practitioner.

## DETERMINATION OF BRONCHOSPASM IN THE GUINEA-PIG

APPLICATIONS OF THE METHOD \*

KARL K KOESSLER, M D, P H D

AND

JULIAN H LEWIS, M D, P H D

CHICAGO

In continuation of studies on the production of amines<sup>1</sup> by bacteria, we devised physiologic methods to supplement the chemical methods that are now being used in this laboratory<sup>2</sup> for the assay of bacterial filtrates. The marked action of amines on smooth muscle, causing violent contractions, forms the basis of such physiologic methods. The adaptation of this action on the smooth muscle of isolated arteries provided one such method, the technic of which is described in a later article. The present article is concerned with still another method, based on the action of amines on the smooth muscle of the bronchi.

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\* From the Otho S. A. Sprague Memorial Institute for Medical Research and the department of pathology of the University of Chicago.

1 Koessler, K. K., and Hanke, M. T. Studies on Proteinogenous Amines. IV, The Production of Histamine from Histidine by *Bacillus Coli Communis*, *J. Biol. Chem.* **39**: 539-584 (Oct.) 1919, Studies on Proteinogenous Amines. XII, The Production of Histamine and Other Imidazoles from Histidine by the Action of Micro-Organisms, *ibid.* **50**: 133-191 (Jan.) 1922, Studies on Proteinogenous Amines. XVII, On the Faculty of Normal Intestinal Bacteria to Form Toxic Amines, *ibid.* **59**: 835-853, 1924, Studies on Proteinogenous Amines. XVII, On the Production of Histamine, Tyramine and Phenol in Common Laboratory Media by Certain Intestinal Micro-Organisms, *ibid.* **59**: 855-866, 1924.

2 Koessler, K. K., and Hanke, M. T. Studies on Proteinogenous Amines. II, A Microchemical Colorimetric Method for Estimating Imidazole Derivatives, *J. Biol. Chem.* **39**: 497-519 (Oct.) 1919, Studies on Proteinogenous Amines. III, A Quantitative Method for Separating Histamine from Histidine, *ibid.* **39**: 521-538 (Oct.) 1919, Studies on Proteinogenous Amines. VII, The Quantitative Colorimetric Estimation of Histidine in Protein and Protein-Containing Matter, *ibid.* **43**: 527-542 (Sept.) 1920, Studies on Proteinogenous Amines. VIII, A Method for the Quantitative Colorimetric Estimation of Histamine in Protein and Protein-Containing Matter, *ibid.* **43**: 543-556 (Sept.) 1920, Studies on Proteinogenous Amines. XIV, A Microchemical Colorimetric Method for Estimating Tyrosine, Tyramine and Other Phenols, *ibid.* **50**: 235-270, 1922, Studies on Proteinogenous Amines. XV, A Quantitative Method for the Separation and Estimation of Phenols Including Phenol, o-, m-, and p-Cresol, p-Oxyphenyl-Acetic, p-Oxyphenylpropionic, and p-Oxyphenyllactic Acids, Tyrosine and Tyramine, *ibid.* **50**: 271-288, 1922.

The various methods that have been previously used for the demonstration of bronchospasm are of two types. The first type makes use of isolated bronchial rings or strips mounted in a suitable medium so that contractions of their muscle are registered by an appropriate lever on a smoked drum. This direct method is modeled after the method of studying contractions of isolated arterial rings and has been used by Trendelenburg,<sup>3</sup> Titone<sup>4</sup> and, more recently, by Macht and Gu-Ching Ting<sup>5</sup> in an extensive study of the antispasmodic action of drugs.

All the other methods are indirect in principle in that contractions of the bronchi are determined from changes in the volume output of the lungs, in the lung volume, in intrapulmonary pressure, in intrathoracic pressure, in thoracic excursions or in the rate of perfusion through the pulmonary vessels. Each of these methods has yielded valuable results in the hands of the investigators who have made use of it. Thus, Brodie and Dixon<sup>6</sup> in their classical studies on the physiology of the lungs employed chiefly the oncometric method, applying it to a single lobe, while Jackson<sup>7</sup> devised a plethysmographic method involving the whole lung, and Auer and Lewis<sup>8</sup> encased the whole animal in a plethysmograph.

None of these methods was suitable for our purpose since we desired a method which is simple enough to be used as a routine procedure, yet which is accurate and which takes advantage of the tremendously reactive pulmonary musculature of the guinea-pig. We finally chose a method which consists of determining changes in intrathoracic pressure and which is an adaptation to the guinea-pig of a device previously used by Jackson<sup>9</sup> for recording changes in the movements of the lungs of dogs.

#### DESCRIPTION OF THE METHOD

A large guinea-pig, weighing from 500 to 800 Gm., is tied, back downward, to a table and anesthetized with ether. The trachea and external jugular vein are dissected out and prepared for ligation. The skull is exposed by making a small incision over the occiput. The bone is perforated with a sharp probe. The medulla and spinal cord are then completely destroyed with a stiff piece of wire. A cannula is promptly tied into the trachea and passive artificial respiration, with positive

3 Trendelenburg, P. *Arch f exper Path u Pharmacol* **69** 79, 1912

4 Titone. *Pflugers Arch f d ges Physiol* **155** 77, 1914

5 Macht, D. I., and Gu-Ching Ting. *J Pharm & Exper Therap* **18** 111, 373, 1921

6 Brodie and Dixon. *J Physiol* **29** 97, 1903

7 Jackson, D. E. *J Pharm & Exper Therap* **4** 1-59, 1912

8 Auer, J., and Lewis, P. A. *Acute Anaphylactic Death in Guinea-Pigs*, *J A M A* **53** 458 (Aug 7) 1909

9 Jackson, D. E. *Experimental Pharmacology*, St. Louis, C. V. Mosby Company, p. 196

pressure, is instituted at once. Compressed air from a tank is sent intermittently into the tracheal cannula by means of an interrupting valve that is controlled by a small electric motor (fig 1). The inflation pressure is measured by a mercury manometer and is controlled by means of an escapement valve which is merely a piece of rubber tubing attached to the side arm of a T tube whose lumen is adjusted with a compression clamp. It is possible to regulate this clamp so that the desired amount of inflation pressure, about 5 cm of mercury, can be

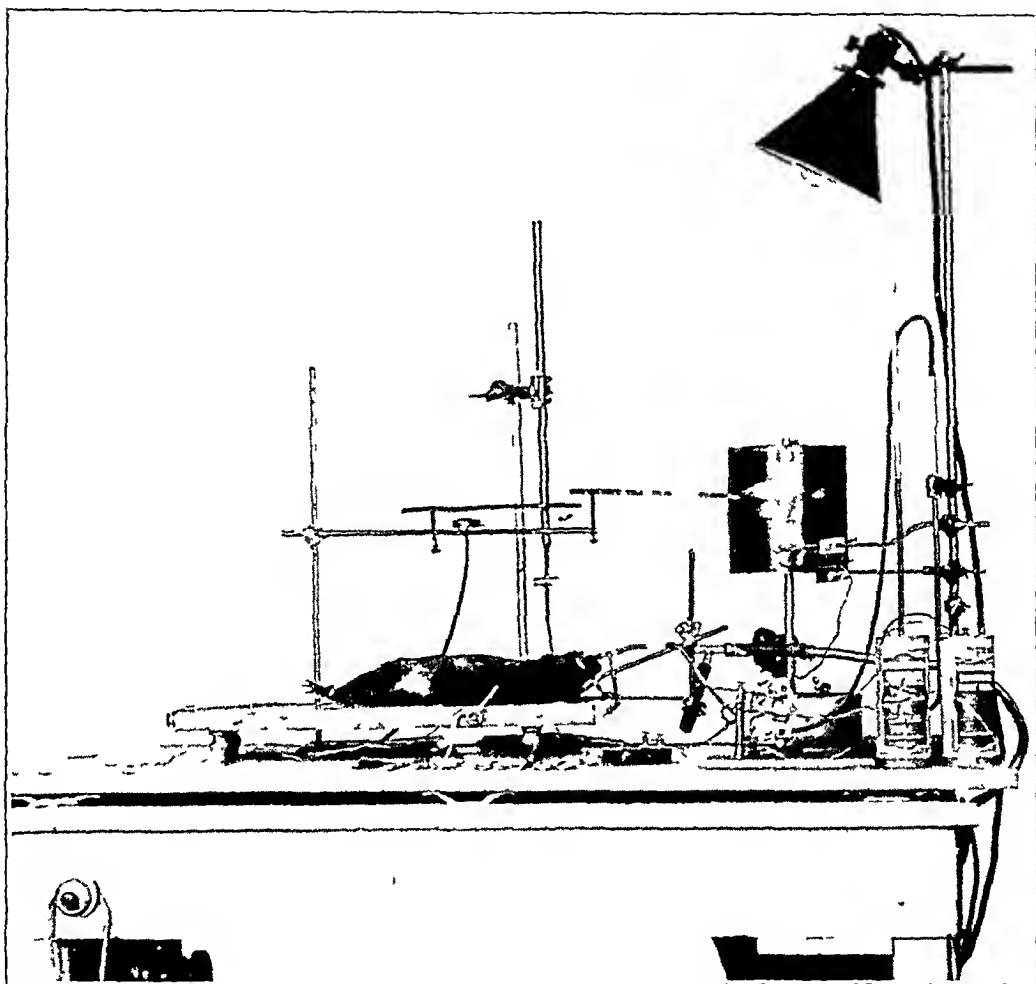


Fig 1—Apparatus for determining bronchospasm in the guinea-pig

obtained. The respiration rate should be about 22 per minute. A small glass T tube is inserted just above the tracheal cannula to permit air to escape easily from the lungs during passive expiration. The heart action continues unimpaired for hours if all these operations have been properly carried out.

A small glass cannula is attached by means of a short piece of rubber tubing to a buret that is filled with physiologic sodium chloride solution. The cannula is filled to the tip with the solution and is tied

into the external jugular vein. Solutions to be tested are injected into the lumen of the rubber tubing with a hypodermic syringe and washed directly into the circulation with physiologic sodium chloride solution from the buret.

Changes in intrathoracic pressure are determined by making a communication between the chest cavity and a sensitive tambour by means of a trocar passed through the chest wall of the guinea-pig. This trocar is a number 13 gage hypodermic needle (about  $3\frac{1}{2}$  inches in length and  $\frac{1}{16}$  inch in diameter). The pointed end is closed with a drop of solder without changing the shape of the point. The wall of the needle is pierced with several small openings covering a space about  $\frac{5}{8}$  inch long near the center (fig 2a). In order to place this trocar in the already prepared guinea-pig, a small tip of the skin over one side of the chest wall is picked up with a pair of forceps and removed with a pair of scissors. The trocar is pushed through the muscular wall and parietal pleura at about the level of the fifth or sixth intercostal space. Feeling

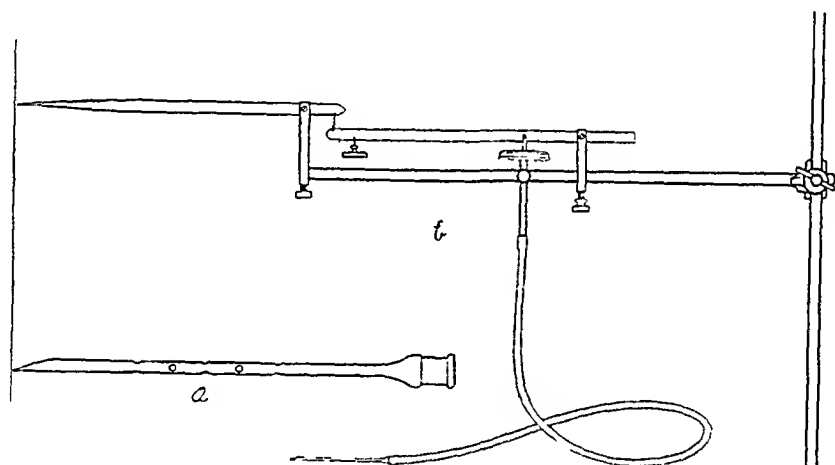


Fig 2—(a) Pertorated trocar, (b) compound writing lever

one's way carefully with the point of the trocar, the lungs, liver, diaphragm and heart are carefully avoided and the needle point is thrust through the pleura and muscular wall of the other side, the skin bulging over it, being cut with scissors. The open end of the trocar is attached to a soft rubber tubing of small caliber and, by means of this, to a Marey tambour. The pleural space, needle lumen (through the openings in the needle wall), rubber tubing and tambour form a closed system and any increase or decrease in pressure in the first produced by changes in lung volume is promptly transmitted to the sensitive rubber diaphragm of the tambour.

The changes in intrathoracic pressure during respiration in the guinea-pig are so slight, due to the small size of the lung, that it was found necessary to amplify the movements of the rubber diaphragm.

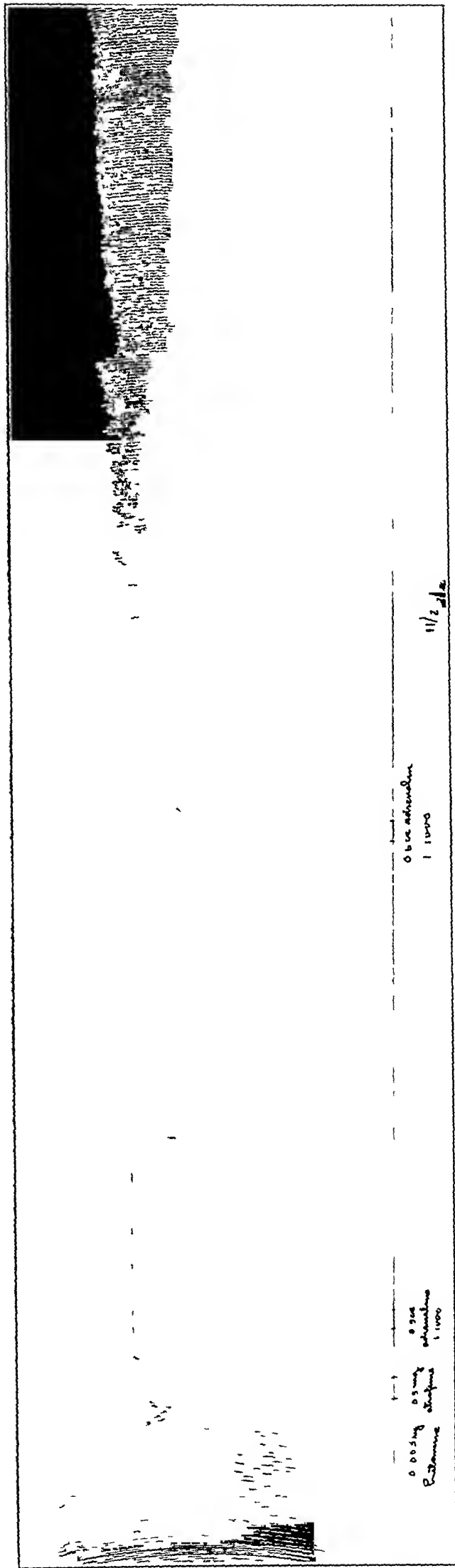


Fig 3—Effect of 0.005 mg of histamine dichloride on the pulmonary excursion A, 0.005 mg of histamine, B, 0.5 mg of atrophine, C, 0.5 cc of epinephrine, 1,000, and D, 0.6 cc of epinephrine, 1,000 (Nov 26, 1923)

In order to do this the lever which rests on the diaphragm is made to actuate another lever instead of writing directly on the smoked drum. The excursion of the second lever is several times greater than that of the first, and under favorable conditions a swing of from 2 to 3 inches is produced by the movements of the guinea-pig's lungs (fig 2 b)

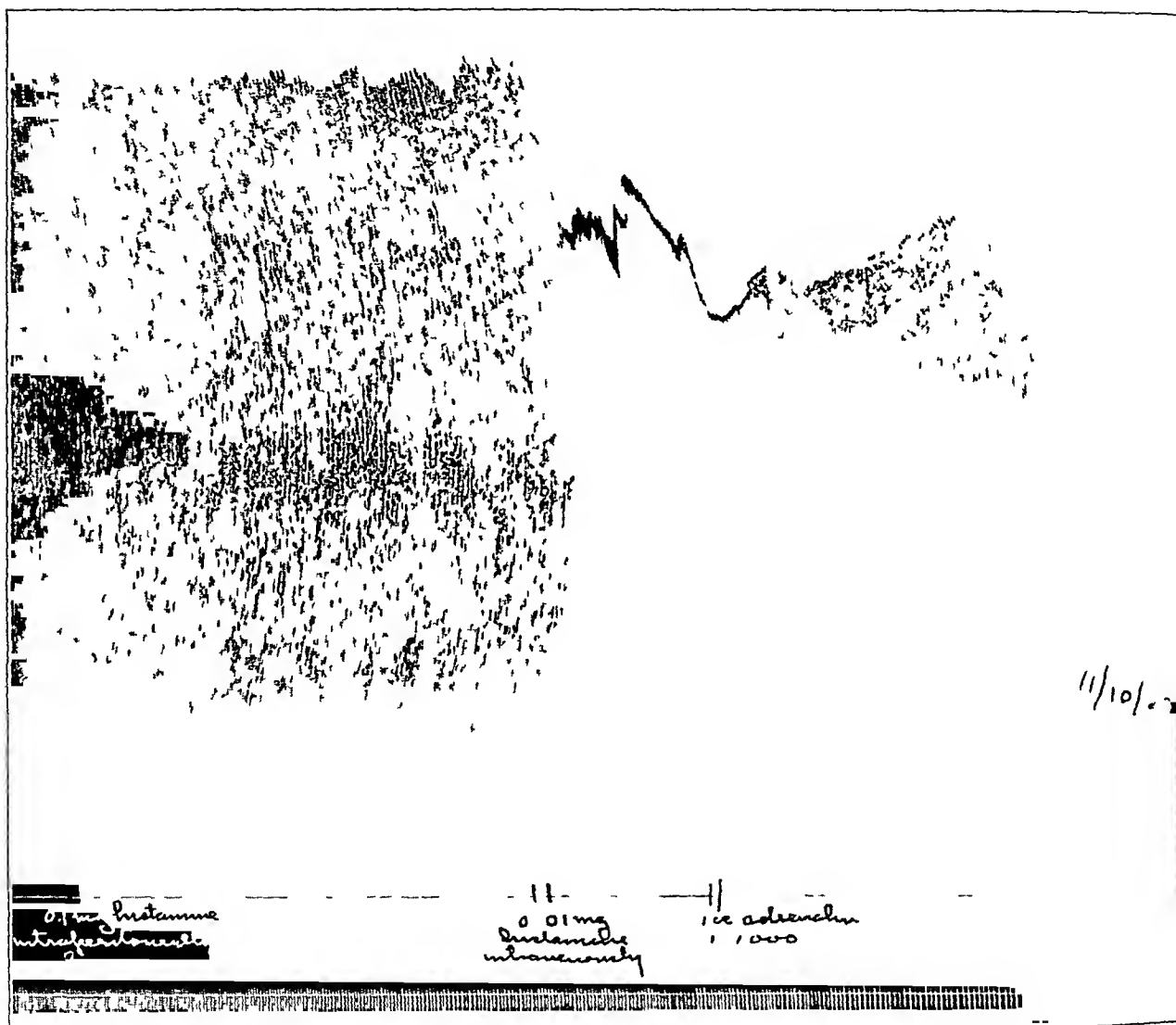


Fig 4—Difference of action of histamine on intraperitoneal and intravenous injection A, 0.1 mg of histamine intraperitoneally, B, 0.01 mg of histamine intravenously and C 1 cc of epinephrine, 1:1,000 (Nov 10, 1923)

Slight changes in the movement of the lungs are plainly registered by changes in the amplitude of the curves. In reading the curves it is to be remembered that a downstroke of the lever represents an inspiration and an upstroke represents an expiration.

## APPLICATION OF THE METHOD

The method was tested with a number of substances known to have a definite peripheral action on the bronchi. Probably the most active of these is histamine. Very small doses of this substance will produce death in a guinea-pig from asphyxia due to a complete blocking of the bronchi as a result of an intense contraction of the bronchial musculature. Figure 3 is a curve showing a severe bronchial spasm produced in a 700 Gm guinea-pig with 0.005 mg of histamine. The spasm was not

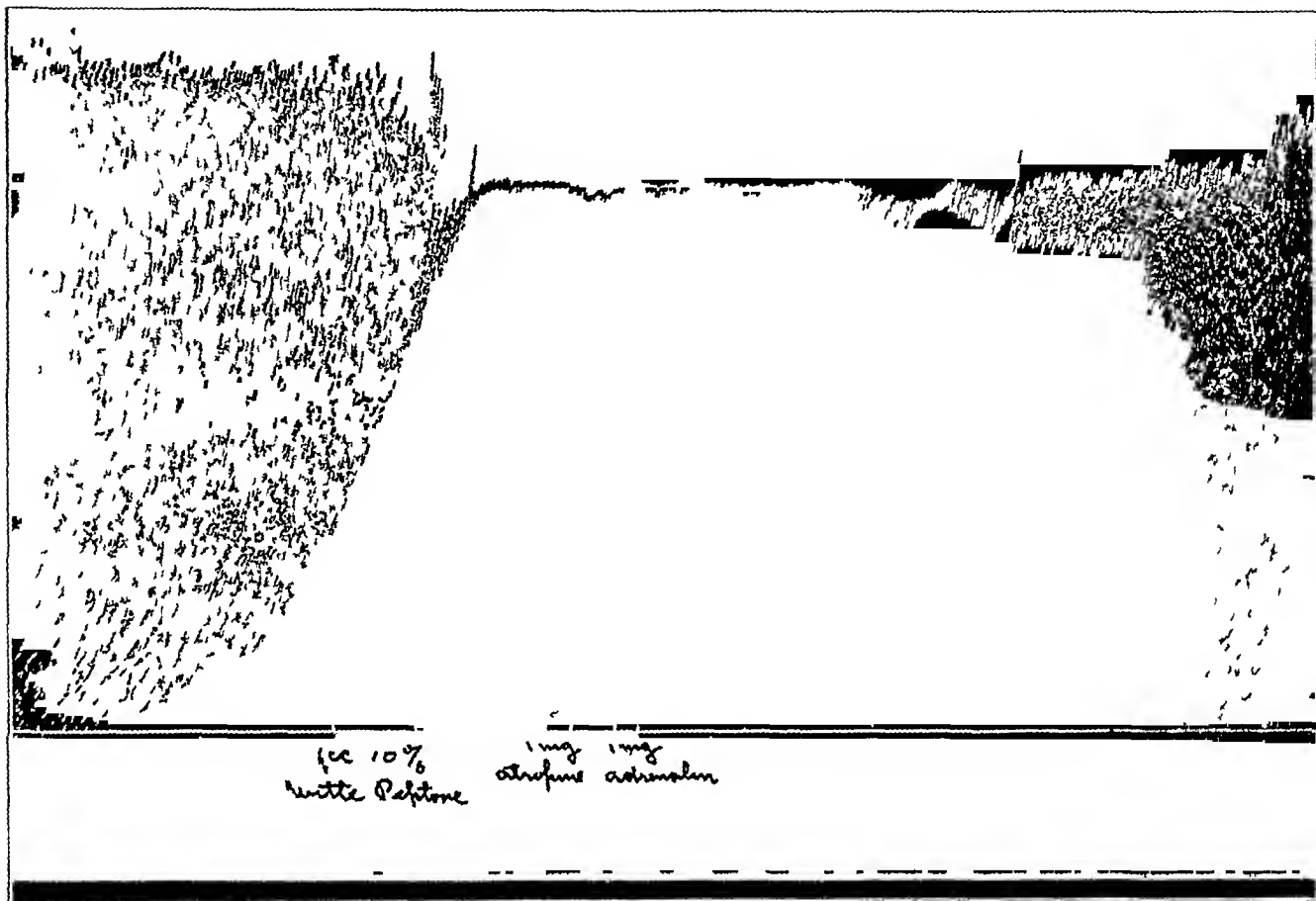


Fig 5—Reaction to Witte's peptone. A, 1 cc of 10 per cent Witte's peptone solution, B, 1 mg of atropine, and C, 1 mg of epinephrine.

released with 0.5 mg of atropine or 0.5 cc of a 1:1,000 solution of epinephrine. It was later released with 0.6 cc of the epinephrine.

Figure 4 shows the difference between the action of histamine injected intraperitoneally and intravenously on the bronchi. When 0.1 mg of histamine is injected intraperitoneally into a guinea-pig, no effect can be noted, while one tenth of this dose, 0.01 mg, injected intravenously, causes the most intense bronchospasm.

Another group of substances of well-known bronchospastic action are the colloidal derivatives of protein known as peptones. Figure 5 shows the reaction of the lungs in the living pithed guinea-pig to the

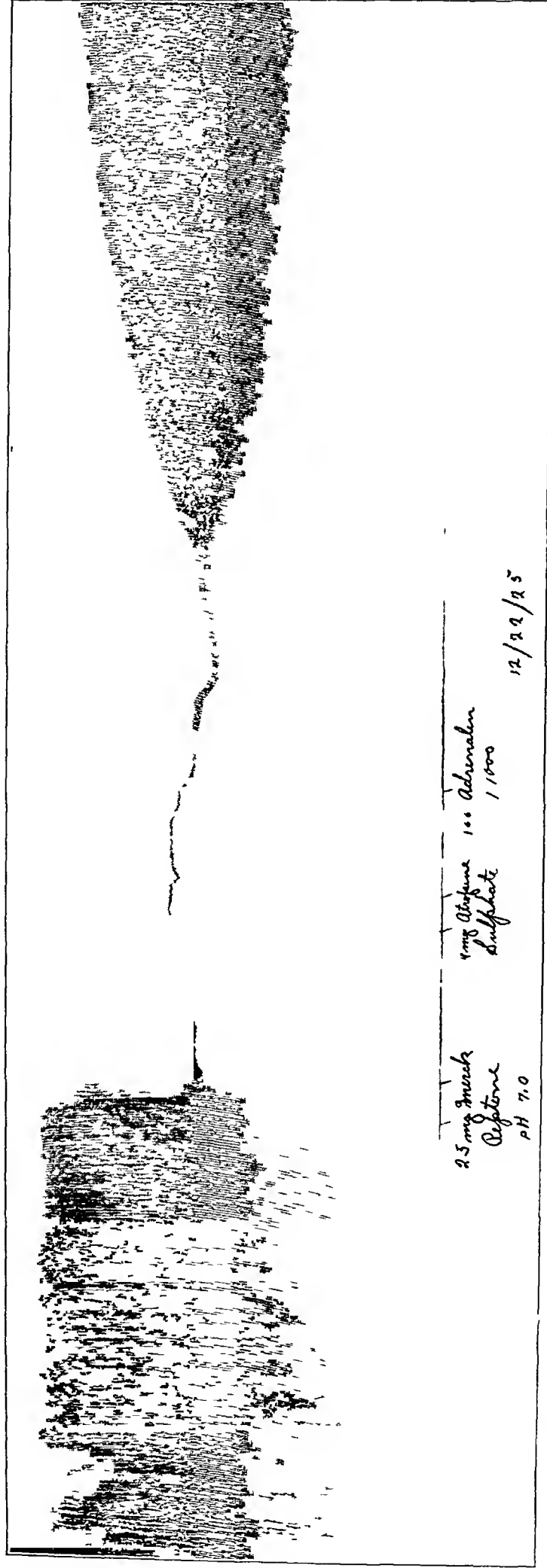


Fig 6—Bronchospasm with Merck's peptone A, 25 mg of Merck's peptone, pH 7.0, B, 4 mg of atropine sulphate, and C, 1 cc of epinephrine, 1 1,000 (Dec 22, 1925)

intravenous injection of 1 cc of a 10 per cent solution of Witte peptone (100 mg) Figure 6 represents a similar curve obtained with 25 mg of Meick's peptone dissolved in 1 cc of salt solution The bronchoconstriction obtained with peptone is not entirely due to its content of histamine, for a histamine-free peptone prepared in our laboratory from fibrin<sup>10</sup> yields a similar pharmacologic reaction on the bronchi in the same dose as Witte peptone (fig 7)

From the inspection of the last three curves it is again evident that the injection of atropine even in large doses was unable to arrest and

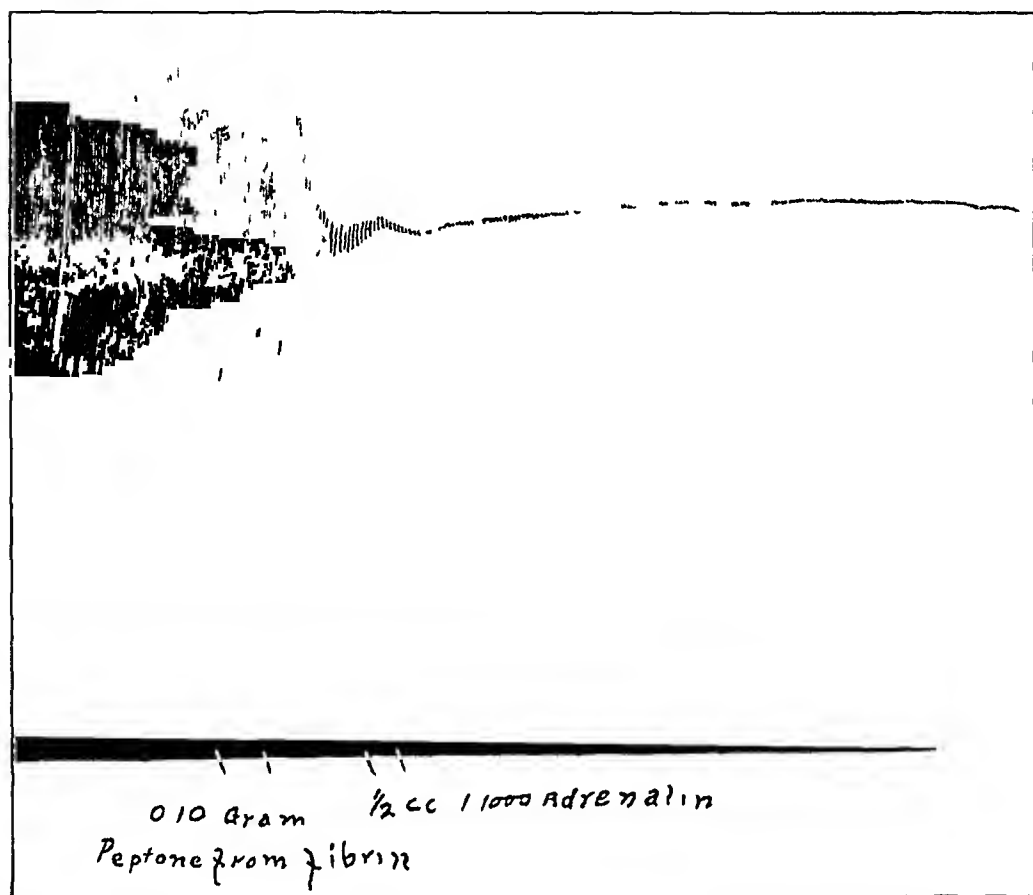


Fig 7—Bronchospasm with a histamine-free peptone prepared from fibrin A, 0.1 Gm of peptone from fibrin, B, 0.5 cc of 1:1,000 epinephrine

release the spasm of the bronchi, whereas 1 cc of epinephrine (1:1,000) sufficed to accomplish this in two cases

Many control experiments have demonstrated that this spasm, if not relieved, commonly leads to the death of the animal by asphyxia The passive insufflation of air through the trachea is incapable of overcoming the resistance offered by the spastic stenosis of the bronchi

<sup>10</sup> Hanke, M. T., and Koessler, K. K. Studies on Proteomogenous Amines. X, The Relation of Histamine to Peptone Shock, J Biol Chem **43** 567-577 (Sept.) 1920

Para-hydroxyphenylethylamine, the amine derived by decarboxylation of tyrosine, is structurally intimately related to epinephrine. This structural relation is associated with certain similarities in physiologic behavior, as in their action on peripheral blood vessels and blood pressure.<sup>11</sup> The action of tyramine on the bronchi, however, is an antagonistic one to that of epinephrine for, whereas the latter produces prompt dilatation of the contracted bronchial muscles and leads thus to disappearance of the pulmonary immobilization, tyramine usually produces bronchospasm. Whether this spasm is due to stimulation of intrapulmonary ganglions, to stimulation of sympathetic bronchoconstrictors or to direct action on the smooth muscle is not entirely established.<sup>12</sup>

In our experiments relatively large doses of tyramine hydrochloride were required to produce changes in the excursions of the lungs—from 75 to 100 mg (fig 8).

Since the experimental analysis of the acute anaphylactic death of the guinea-pig by Auer and Lewis,<sup>13</sup> Biedl and Kraus<sup>14</sup> and Anderson and Schultz,<sup>15</sup> it can be accepted as proved that death in the guinea-pig is primarily due to the asphyxia produced by a spastic stenosis of the bronchioles. This conclusion is also arrived at by Dale,<sup>16</sup> who in a recent investigation of anaphylaxis and anaphylatoxins after studying changes in lung volume, says, "There is hardly room for doubt that the (bronchial) obstruction in the anaphylactic reaction is due almost entirely to plain muscle contraction."

Figure 9 represents the respiratory tracing with our method from a case of typical anaphylaxis to horse serum. The guinea-pig had been sensitized by the subcutaneous injection of 0.01 cc of horse serum. The reaction followed an intravenous injection of 0.5 cc of horse serum. Complete cessation of all pulmonary excursions soon took place, although the same quantity of air was delivered into the trachea as before injection. Necropsy performed while artificial respiration was continued showed the lungs maximally inflated and entirely immobile. The heart continued to beat for a short while. Another instance of horse serum anaphylaxis is shown in figure 10. The complete abolition of the pul-

11 Barger and Dale. *Arch f exper Path u Pharmacol* **61** 113 (Sept) 1909

12 Baehr and Pick. *Arch f exper Path u Pharmacol* **74** 41, 1913

13 Auer and Lewis. *J Exper Med* **12** 15, 1910

14 Biedl and Kraus. *Handbuch der Immunitats forschung of Kraus-Levaditi Ergänzungs*, **1** 255-290, 1911

15 Anderson, J F, and Schultz. *Proc Soc Exper Biol & Med* **7** 32, 1910

16 Dale, H H, and Kellaway, C H. *Anaphylaxis and Anaphylatoxins*, *Philosophical Tr* **211** 273 1922, especially pp 304-306

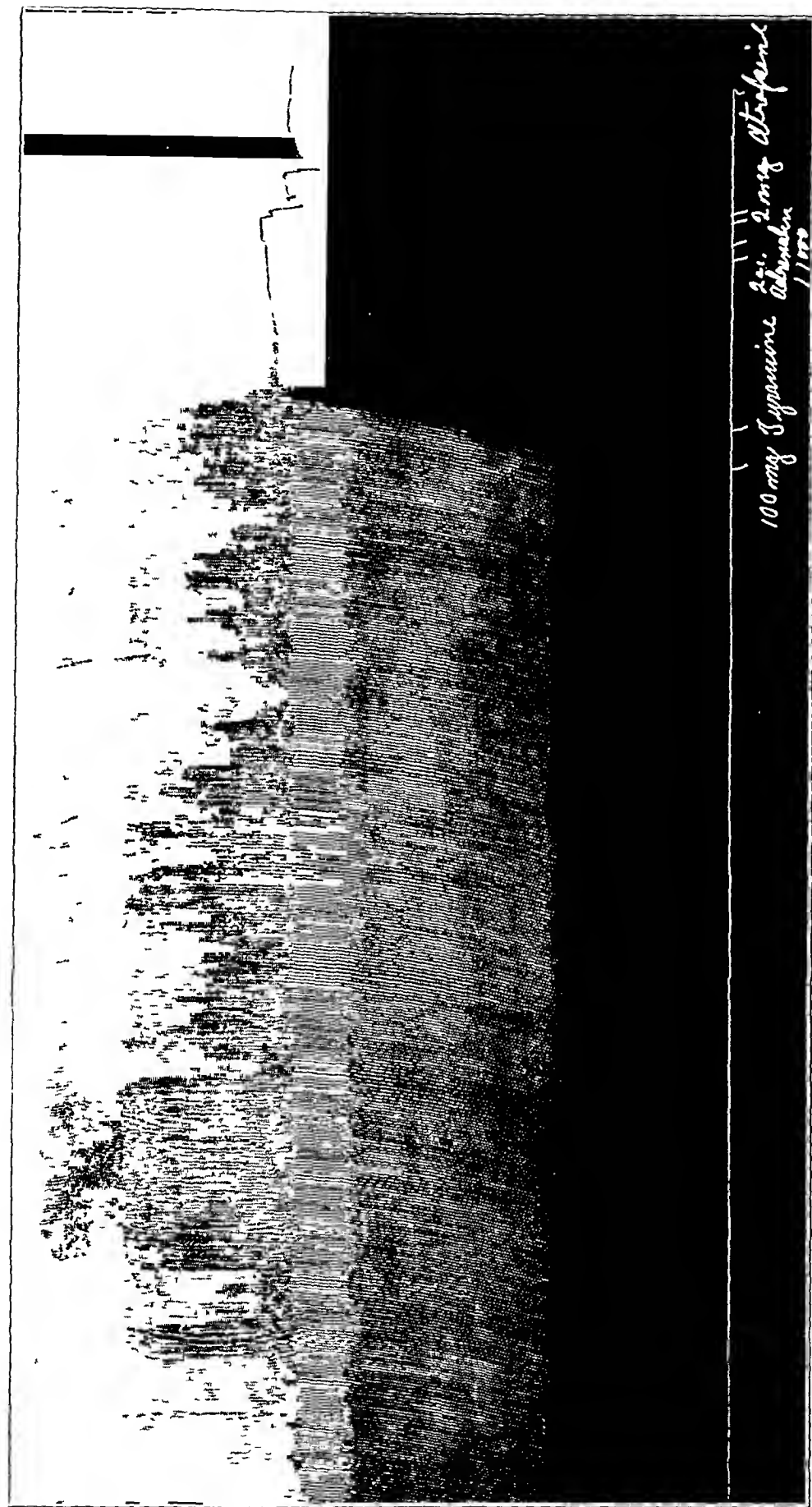


Fig 8—Bronchospasm with parahydroxyphenylethylamine -4, 100 mg of parahydroxyphenylethylamine, B 2 cc of 1 1,000 epinephrine, and C mg of atropine (Jan 4, 1926)

Artificial respiration  
continued showing inflated and  
entirely immobile heart was  
still beating

in horse serum intravenously

Guinea pig sensitized to proteins  
from horse serum

10/28/23

Fig 9—Typical anaphylaxis in guinea-pig sensitized to proteins from horse serum A, 0.5 cc of horse serum intravenously (Oct 28, 1923) Necropsy while artificial respiration was continued showed lungs inflated and entirely immobile, the heart was still beating

monary oscillations, which would probably have led to the death of the animal by asphyxia, was released by the intravenous injection of 0.4 mg of atropine sulphate. Figure 11 shows a curve of the bronchial constriction in the guinea-pig in anaphylaxis to ragweed pollen.<sup>17</sup> Figure 12 represents an instance of passive anaphylaxis to ragweed pollen.

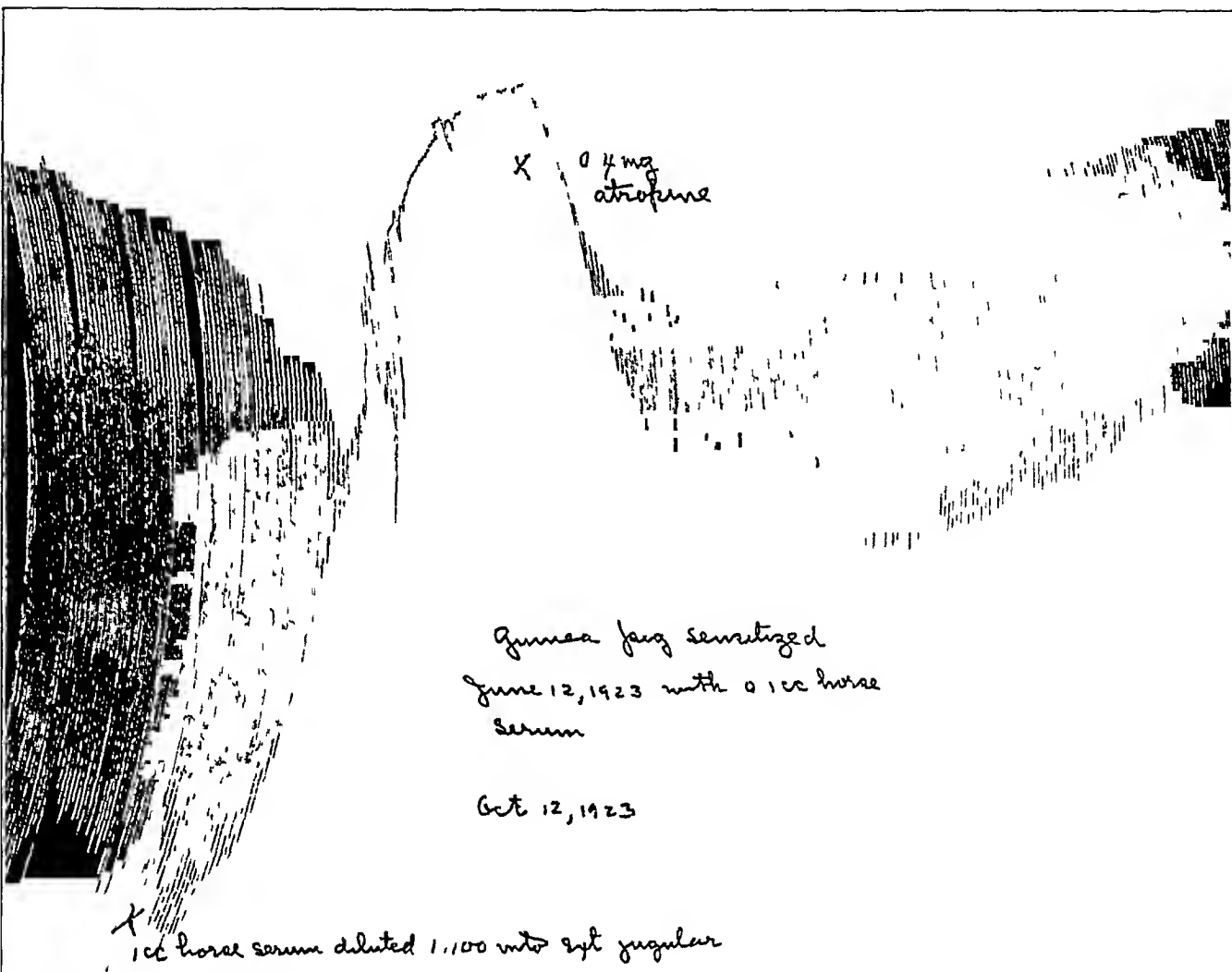


Fig 10—Typical horse serum anaphylaxis in guinea-pig sensitized June 12, 1923, with 0.1 cc of horse serum. A, 1 cc of horse serum diluted 1:100 injected into external jugular vein, B, 0.4 mg of atropine (Oct 12, 1923)

It has been shown that a large number of substances, crystalline as well as colloid in nature, are able to produce on first injection into the guinea-pig a group of symptoms which are practically indistinguishable from those due to true antigen-antibody anaphylaxis. Fall in blood

17 Huber, H. L., and Koessler, K. K. The Antigenic Property of Pollens. Arch Int Med 36 751-761 (Dec) 1925

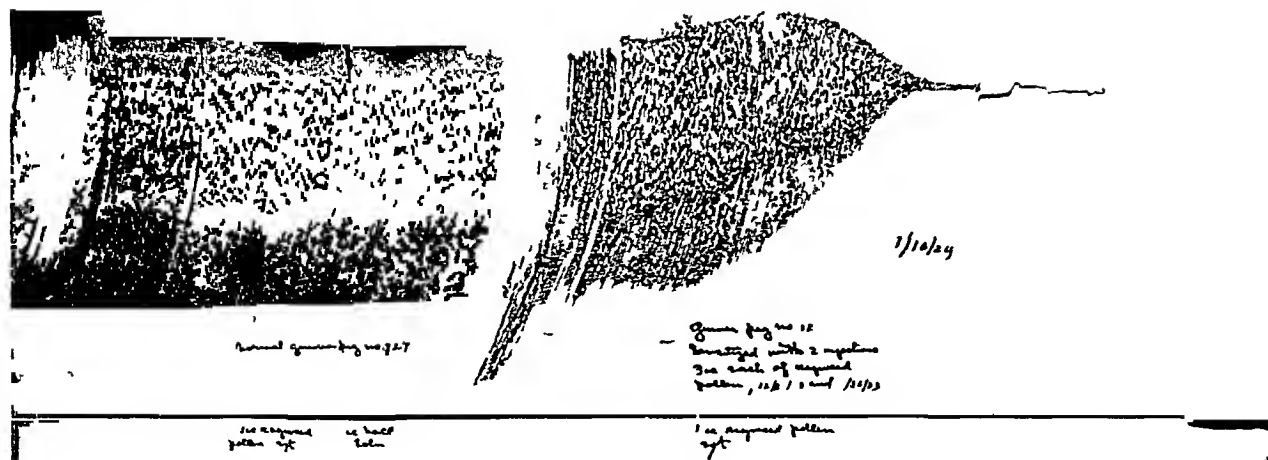
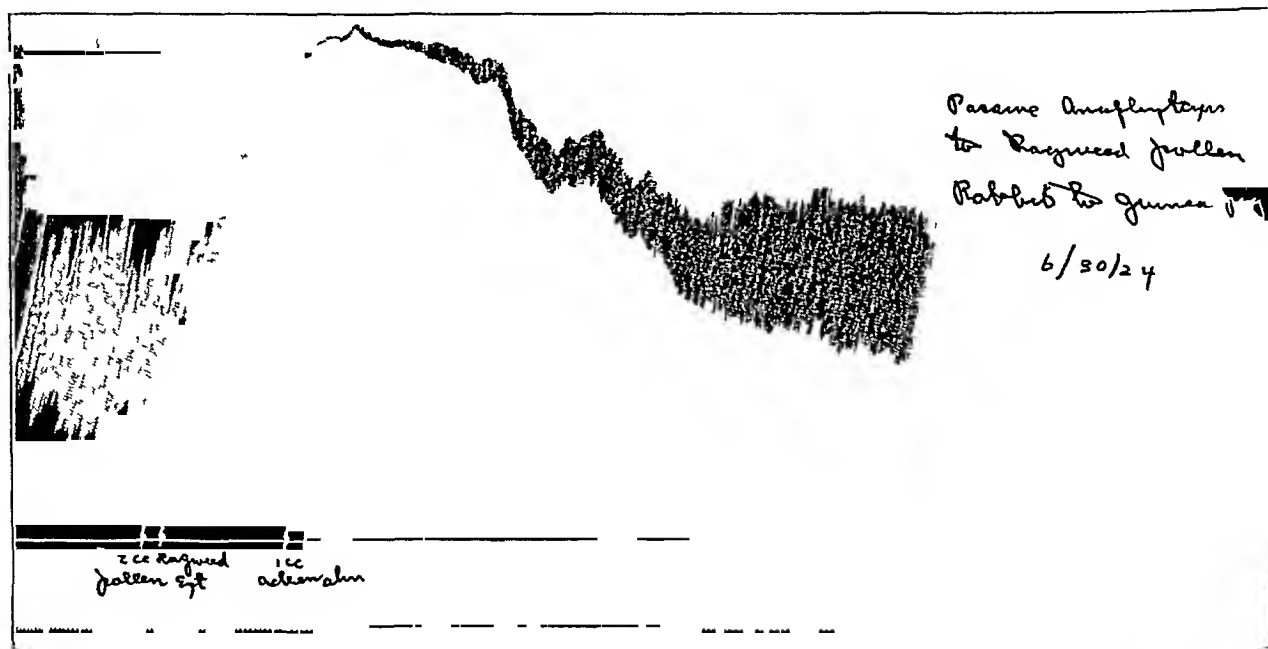


Fig 11—Typical anaphylaxis to ragweed pollen

Fig 12—Passive anaphylaxis to ragweed pollen, rabbit to guinea-pig  
A 2 cc of ragweed pollen extract, and B, 1 cc of epinephrine (June 30, 1924)

pressure, leukopenia, diminished coagulability of the blood and immobilization of the lungs are all present. The important difference between these reaction phenomena and true anaphylaxis lies in the fact that these substances produce the symptoms on first injection in the normal non-sensitized animal. A thorough study of the action of such substances

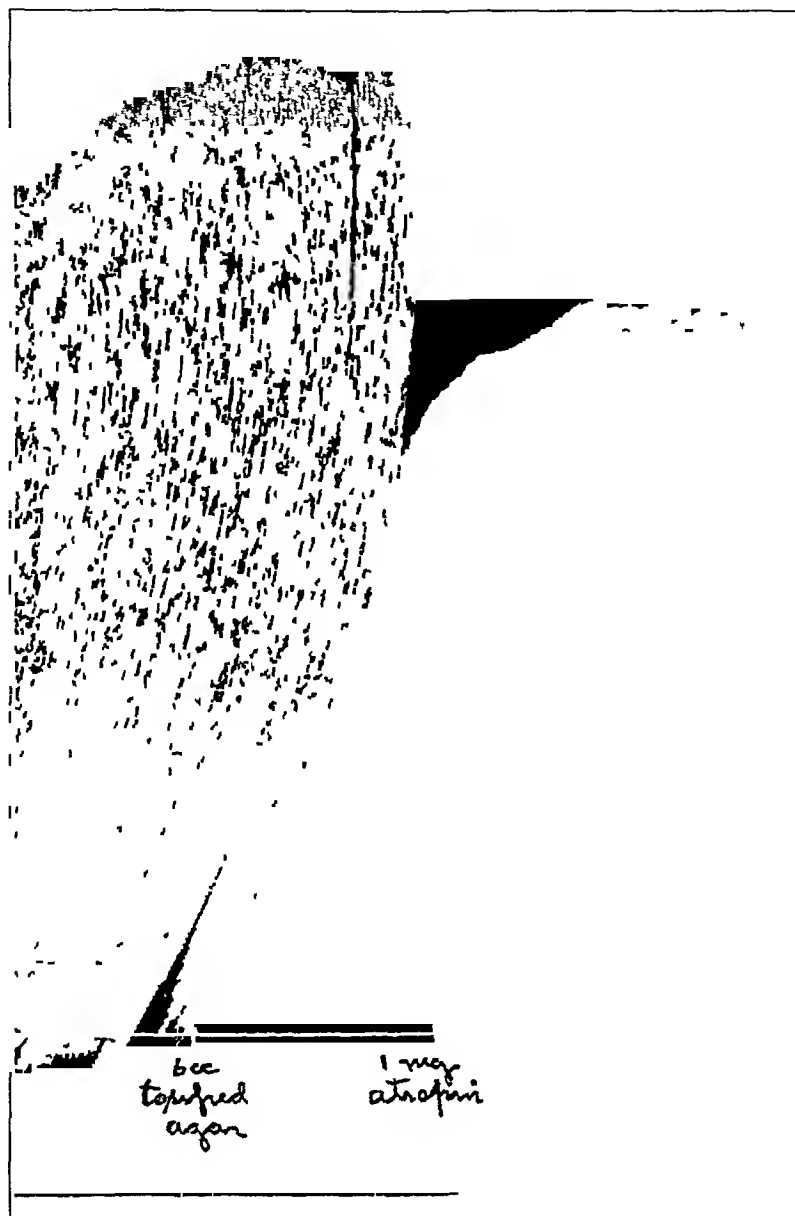


Fig. 13—Anaphylactoid reaction with toxified agar. *A*, 6 cc of toxified agar, *B*, 1 mg of atropine.

has been made by Karsner and Hanzlik,<sup>18</sup> who call these phenomena "anaphylactoid reactions." The methods used by them in the study of the respiratory disorders and pulmonary changes following the injection

<sup>18</sup> Hanzlik, P. J., and Karsner, H. T. *J. Pharm. & Exper. Therap.* **14**, 379-492 (Jan.) 1920.

tion of the various colloid substances used were perfusion of the lungs according to the method of Baehi and Pick,<sup>12</sup> and direct examination microscopic and macroscopic, of the lungs. The mechanism of the action of the active agents in the production of the permanent distention of the lungs in the phase of inspiration they ascribe to occlusion of the pulmonary capillaries by thrombi of agglutinated corpuscles and plate-

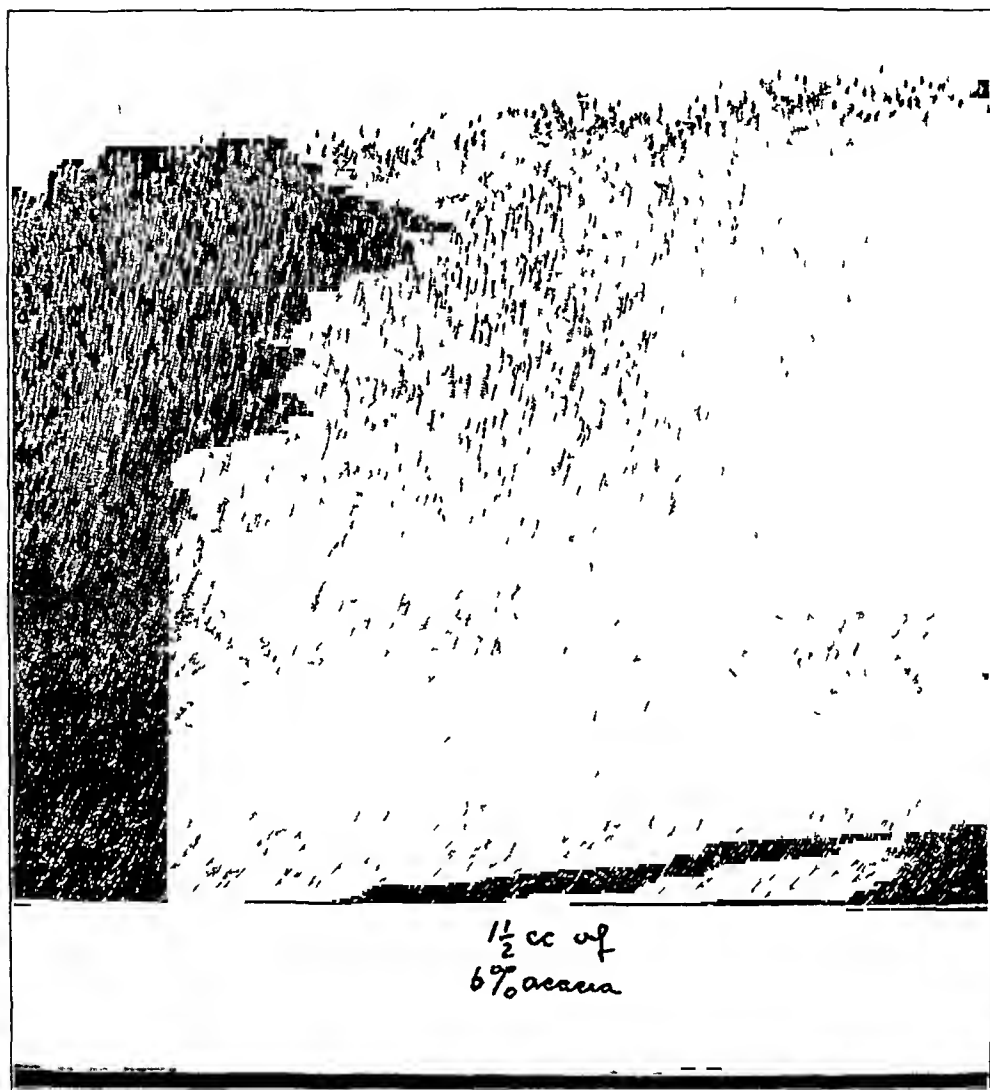


Fig 14—Absence of anaphylactoid reaction with acacia A, 15 cc of 6 per cent acacia solution

lets, which produces bronchoconstriction. This bronchoconstriction, produces with agar solgel and other colloids, differs in origin from that produced by true anaphylaxis, peptone or histamine. It is not due to direct stimulation of the bronchial musculature or parasympathetic endings, since the effects are not antagonized by atropine or papaverine. It is suggested that embolism in the pulmonary vessels compresses the

bionchioles and thus leads to passive bionchostenosis. Our method should be an additional aid in properly evaluating the part played by true bionchoconstriction resulting in complete permanent distention of the lungs in the phase of inspiration. The pithing of the animal would exclude the central influences to which Karsner and Hanzlik ascribe certain pulmonary reactions. The results obtained with our method would seem, on the whole, to corroborate the correctness of the conclusions of Karsner and Hanzlik.

Figure 13 shows the effect of the intravenous injection of 6 cc of toxified agar in the guinea-pig. The toxified agar was prepared according to Karsner and Hanzlik<sup>18</sup>. The respiratory excursions of the lungs were completely arrested with permanent distention of the organ. The intravenous injection of 1 mg of atropine sulphate follow-

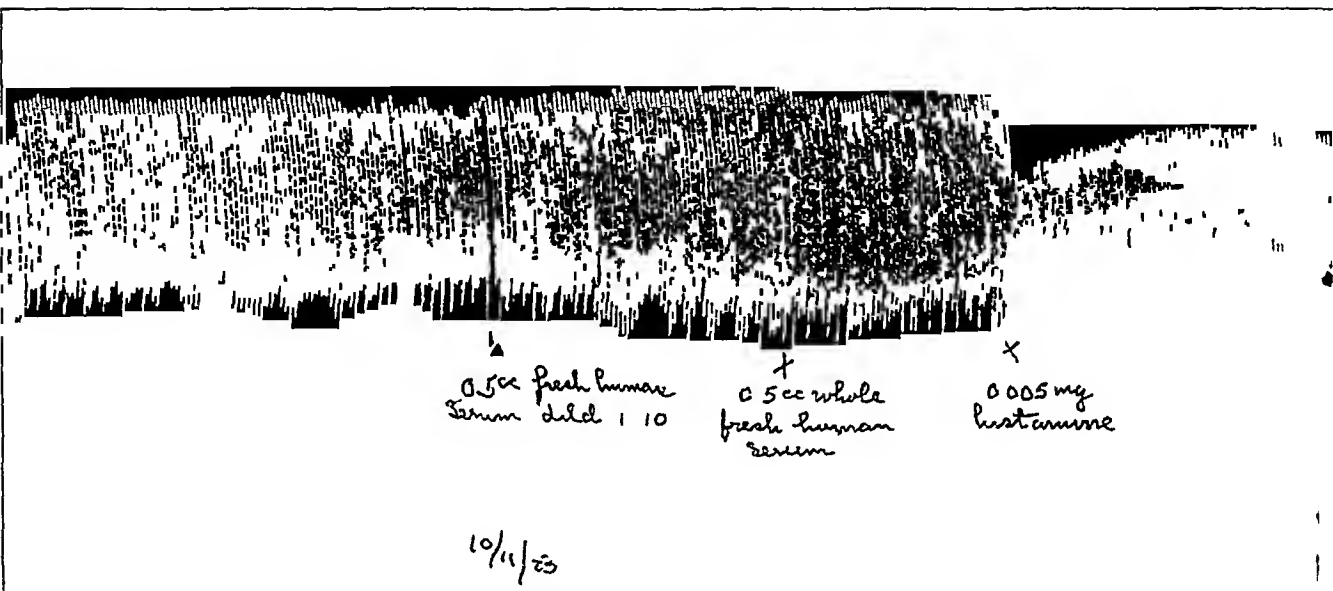


Fig 15—Absence of anaphylactoid reaction to fresh human serum. A, 0.5 cc of fresh human serum diluted 1:10, B, 0.5 cc of whole fresh human serum, and C, 0.005 mg of histamine (Oct 11, 1923)

ing the injection of the agar was not able to relieve the respiratory distress and remove the pulmonary distention.

The effect of toxified agar in the pithed animal is proof that the seat of its action lies in the periphery, but the absence of relief by atropine seems to exclude the smooth muscle system of the bronchi as the primary seat of stimulation.

The injection of 1.5 cc of 6 per cent acacia solution into the jugular vein of the living pithed guinea-pig was without action on the respiration of the animal (fig 14).

No effect was obtained with 0.5 cc of fresh human serum injected intravenously (fig 15).

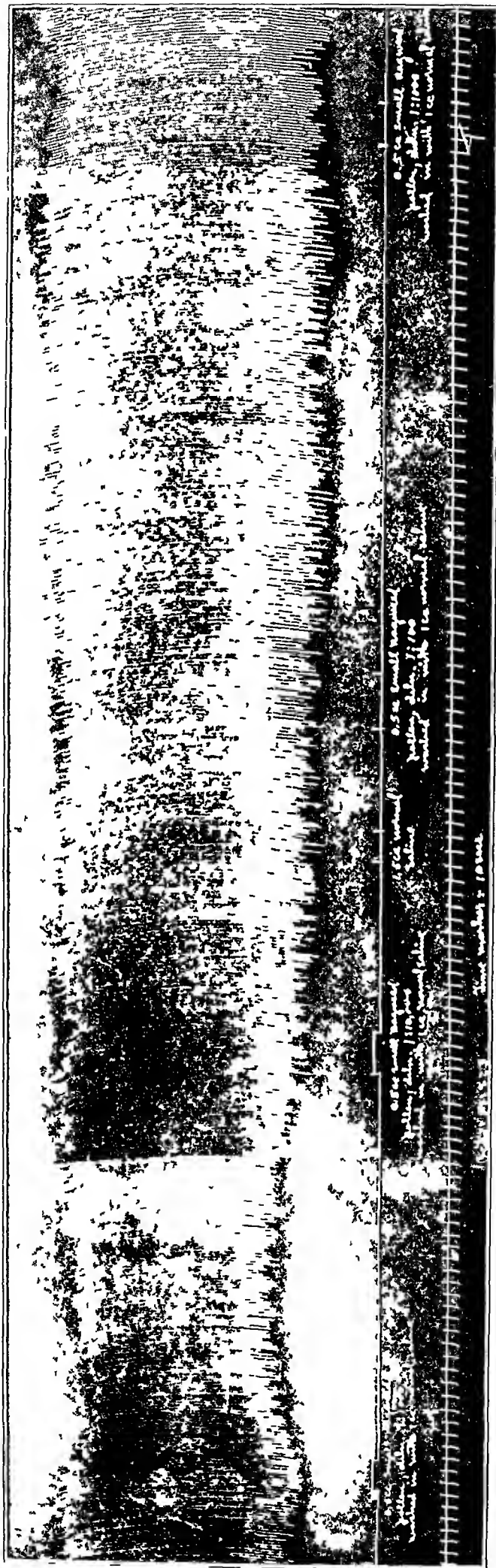


Fig 16—Absence of anaphylactoid reaction with pollen extracts A, 0.5 cc of small ragweed pollen, diluted 1 1,000, washed in with 1 cc of physiologic sodium chloride solution, B, 0.5 cc of small ragweed pollen, diluted 1 1,000, washed in with 1 cc of physiologic sodium chloride solution, C, 15 cc of physiologic sodium chloride solution, D, 0.5 cc of small ragweed pollen, diluted 1 100, washed in with 1 cc of physiologic sodium chloride solution, and E, 0.5 cc of small ragweed pollen, diluted 1 1,000, washed in with 1 cc of physiologic sodium chloride solution (Oct 15, 1923) Time marker, 10 seconds

In a recent article on the antigenic action of pollen by Koessler and Huber<sup>17</sup> it was shown that typical anaphylaxis can be produced with pollen extracts in guinea-pigs under proper experimental conditions. A necessary preliminary to this investigation was the proof that the intravenous injection of the pollen extracts used does not give rise to changes in pulmonary movements in the nonsensitized animal, especially since Karsner and Hanzlik, working with an entirely different technic, reported respiratory disturbances which they ascribe to hemorrhages and conglutination thrombi.

Figure 16 shows that even 0.5 cc. of a 1:100 dilution of ragweed pollen extract does not produce the slightest change in the pulmonary excursions of a pithed guinea-pig.

Figure 11 demonstrates that bronchoconstriction is brought about promptly under the same experimental conditions in the sensitized animal.

#### CONCLUSIONS

In the method for graphic demonstration of bronchospasm in the guinea-pig described, the procedure is simple and can be carried out as a routine procedure in any laboratory.

A number of substances (histamine, para-hydroxyphenylethylamine and various peptones) of known bronchospastic activity were tested with this technic.

The method has proved itself a valuable aid in the experimental analysis and diagnosis of anaphylaxis and anaphylactoid phenomena.

# DEMONSTRATION OF ARTERIAL CONSTRICTION IN VITRO

## A NEW METHOD<sup>\*</sup>

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AND

KARL K KOESSLER, M D, P H D

CHICAGO

The most characteristic and constant feature of the anaphylactic reaction is the contraction of smooth muscle. It is this manifestation which accounts for the sudden and dramatic clinical picture that is ordinarily produced in anaphylaxis, especially in the common laboratory animals. According to the animal used, either the contraction of the smooth muscle of one system of organs is more massive than that of another, or, because of different anatomic relations, more profound symptoms are produced. Whether or not there is a participation to some extent of all the smooth muscle tissue in the body, or whether there is a selective action for certain groups, cannot be decided at present, either because of the nonappearance of clinical symptoms which may identify the participation of certain organs, or because of the lack of suitable methods to demonstrate the in vitro response of the smooth muscle in all organs.

Because of certain similarities that exist between the anaphylactic reaction and the action of certain amines, e. g., histamine and tyramine hydrochloride, the same problems as to the localization of action on smooth muscle likewise apply to the amine action as well as to anaphylaxis. It can be demonstrated by the Dale<sup>1</sup> technic that the uterine and intestinal smooth muscle of the guinea-pig is contracted in anaphylaxis and by the application of histamine and tyramine hydrochloride. The active participation of the smooth muscle of the bronchi in the anaphylactic and amine reactions can be demonstrated by the technic of Koessler and Lewis<sup>2</sup> but the great bed of smooth muscle, the vascular system, has not been studied with the same exactness with which the uterine, intestinal and bronchial musculature have been investigated. It is true that the effect of anaphylaxis and of the amines on the blood pressure is known, but changes in blood pressure are the result of a complicated reaction and do not permit an analysis of the reaction of vascular smooth

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<sup>\*</sup> From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

<sup>1</sup> Dale and Laidlaw. *J. Pharm. & Exper. Therap.* **4**: 75, 1912.

<sup>2</sup> Koessler, K. K., and Lewis, J. H. The Determination of Bronchospasm in the Guinea-Pig. *Arch. Int. Med.* **39**: 163, 1927.

muscle per se. For example, the reaction of an isolated artery to histamine would lead one to expect a pressor reaction in vivo instead of the marked depressor effect that is characteristic of this substance.

Studies of the action of substances directly on the arteries have usually been made by the perfusion method, which consists of forcing through the blood vessels of an organ a fluid that contains the material to be studied. The effect is determined by the changes noted in the rate of outflow. This procedure has given valuable information to many investigators and is one of the standard methods in physiologic work. It has, however, certain drawbacks, and results obtained by the method show occasional inconsistencies. Macht<sup>3</sup> has pointed out that errors arise from the variation in the method of inserting the cannulas and from changes that occur in the parenchyma of the organ during perfusion. It is well known that the tissues of organs under the artificial conditions of perfusion often swell to such an extent that circulation through the blood vessels is completely blocked.

Myer<sup>4</sup> devised a technic of studying the reaction of isolated blood vessels which is comparable to that used by Schultz<sup>5</sup> and Dale<sup>1</sup> for the isolated uterus. A cross-section of a large artery from an animal such as the cow is divided so as to form a strip and is mounted in the Dale apparatus. In order to use smaller arteries, a series of small rings of arterial wall is united by means of loops of thread, thus making a chain of them. When mounted in the Dale apparatus a constriction of the circular fibers of each ring will produce a shortening of the whole chain. Voegtlin and Macht<sup>6</sup> improved this technic and described the procedure of applying a stretching load to the chain of arterial rings which overcomes the marked initial tonus of an isolated artery. The stretched chain is provided with a smaller lifting load, which remains attached during the experiment. Our results with this method were not satisfactory, first, because it is a rather tedious operation to tie together four or more small rings of an artery such as a pig's carotid, second, because the threads used to tie the rings together either stretch or cut the arterial rings when subjected to the weights necessary to overcome the primary tonus, or unless great care is taken in tying them, often pull apart when weighted. There is a marked distortion of the rings and an unequal distribution of the force to all the muscle fibers of the preparation as a result of the stretching. Again, it is difficult to get the required relation between stretching load and lifting load. It is different for each preparation, and if it is not properly adjusted, the line produced by the writing lever is not straight, it shows either a

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3 Macht. *J. Pharm. & Exper. Therap.* **6** 13, 1914.

4 Myer. *Ztschr. f. Biol.* **48** 352, 1906.

5 Schultz. *Hygiene Laboratory Bulletin*, no. 80, 1912.

6 Voegtlin and Macht. *J. Pharm. & Exper. Therap.* **5** 79, 1913.

gradual return of the original tonus on a continuous stretching. The response of this preparation to such active vasoconstrictors as epinephrine and histamine is sluggish and protracted, and is not comparable to the activity shown by the uterus strip or segments of intestines. The uncertainty of this method has been pointed out previously by Muller.<sup>7</sup>

After many efforts to improve this technic and make it adaptable to our purpose we finally devised another method in which the arterial preparation is a continuous band of tissue representing a considerable length of artery, so prepared that the circular musculature is made

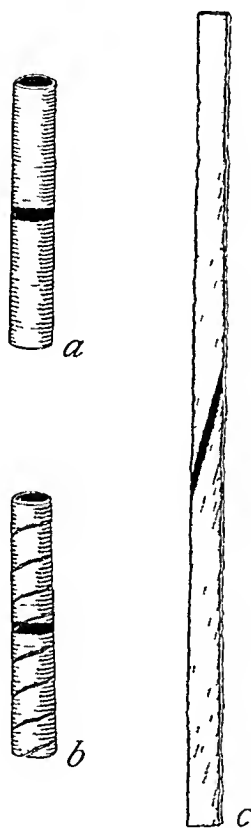


Fig. 1—Steps in the preparation of an artery to demonstrate vasoconstriction. The heavy black marks represent the direction of the circular muscle fibers before and after the artery is cut and unrolled, the length of *c* is that obtained by starting with the length of *a*.

to be perpendicularly, when it contracts, a shortening of the preparation occurs. An artery, such as the pig's carotid, is trimmed of all loose connective tissue. One blade of a small pair of scissors is inserted into one end and a winding spiral incision is made the whole length of the artery. The scissors are slanted so that the incision at one place is about one-eighth inch (0.3 cm.) below the incision above it. When the incision is completed the preparation resembles the paper winding that is

<sup>7</sup> Muller, F. Arch. f. Anat. u. Physiol., 1906, supp. vol., p. 411.

removed from a wax pencil. It is now unfurled by running the whole ribbon between the fingers and slightly stretching. This process causes the circular muscle fibers to run in the direction of the length of the ribbon (fig. 1). A thread is now tied on both ends. A length about 4 inches (10 cm) of the prepared artery is used, although a longer or shorter one may serve. We usually employ a double strip as it seems to give a sharper reaction and to last longer. The strip is now mounted in the chamber of the Dale apparatus, which contains Locke's solution through which oxygen is bubbled. The lever is attached so that it is in the position of maximal contraction. A 20 Gm weight is applied to the lever for about ten minutes after which a 2 Gm weight is attached. The lever is adjusted and the weight shifted until there is no movement up or down and a straight line is written on a slowly moving drum. The preparation is now ready for use. Substances that produce vaso-

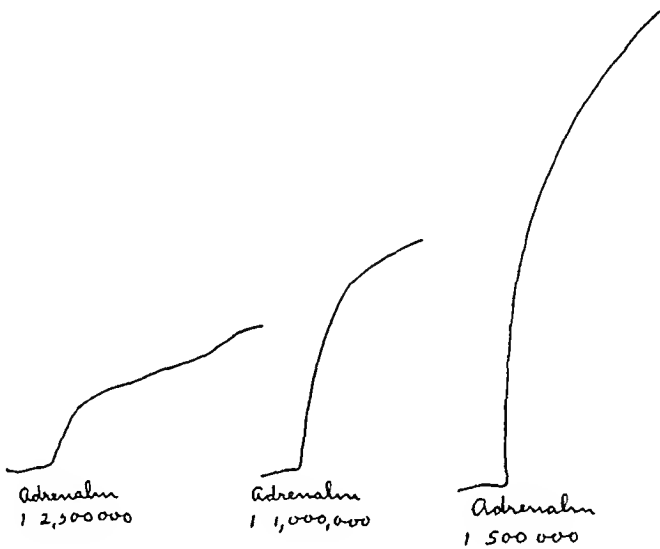


Fig. 2—Arterial constriction in vitro due to epinephrine

constriction will cause, when added to the liquid in the chamber, a sudden sharp movement of the lever, the height of which depends on the concentration of the active substance. If the contraction has been large the original position of the lever is recovered slowly. Our procedure is to note the height to which the curve goes, then wash the preparation with three changes of Locke's solution, after which the 20 Gm weight is applied for about five minutes. This can be done without removing the 2 Gm weight. The preparation is now ready for use again. This can be repeated ten or fifteen times before it gives out. The first sign of fatigue of the muscle is a failure to rise to its normal level after removal of the 20 Gm weight.

It is our custom to obtain from twelve to fifteen pigs' carotids from the stockyards and place them immediately in a bottle of Locke's solution containing a small amount of pig's blood. If the bottle is kept cold and

the Locke's solution aerated every day with oxygen, the arteries will remain usable for at least one week. When in a good condition the artery has a small lumen and appears as a rigid pink tube when trimmed of excessive connective tissue. As the arteries get old they become white, the lumen flattens out and they are flabby. When in such condition, they should be discarded.

This method is sensitive to vasoconstrictors. Figure 2 shows curves obtained with various dilutions of epinephrine hydrochloride, figure 3,

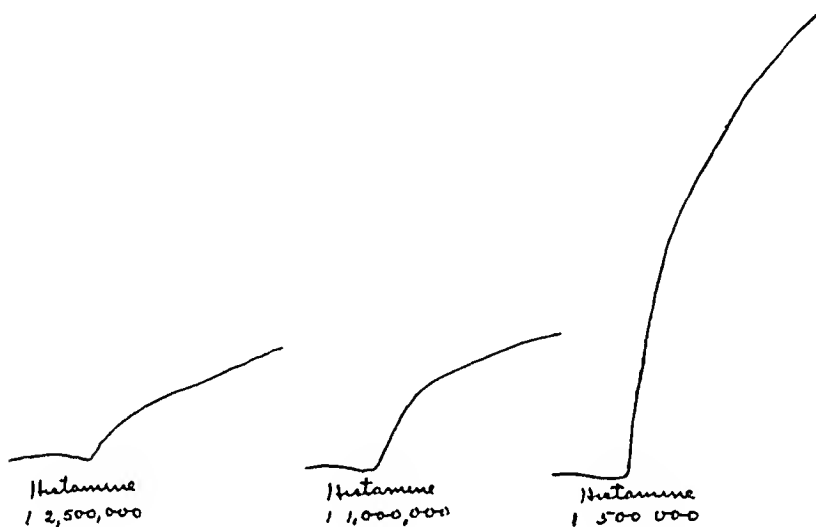


Fig 3—Arterial constriction in vitro due to histamine

similar curves obtained with various dilutions of histamine. But even concentrations of 1 10,000,000 of epinephrine hydrochloride, as well as of histamine, give definite and clear cut contractions. Tyramine hydrochloride is less active, the limits of its activity being from about 1 500,000 to 1 1,000,000.

The interest in guanidine and its methyl derivatives and their possible relation to arterial hypertension has recently been revived through the work of Major.<sup>8</sup> Rather high concentrations of these substances, however, are required to show any effect on the isolated arteries in vitro, a reaction that corresponds well with their behavior in the living animal (fig 4).

The constancy and uniformity of the response is remarkable. The same concentration of vasoconstrictor substance will give the same amount of contraction with the same preparation time after time.

8 Major, R. H., and Stephenson, W. The Effect of Methyl Guanidine on the Blood Pressure, *Bull. Johns Hopkins Hosp.* **35** 140 (May) 1924, Further Observations on the Elevation in Blood Pressure Produced by Guanidine Compounds, *ibid.* **35** 186 (June) 1924, The Excretion of Guanidine Bases in Two Cases of Arterial Hypertension with Reduction in Blood Pressure, *ibid.* **36** 357 (May) 1925.

We have used the method extensively to study the vasoconstrictor action of bacterial poisons, a problem that has been the subject of work for years in this laboratory. Bacteria are grown in liquid mediums of various compositions and under different conditions. The Bekefeld filtrates of these cultures are tested in a routine manner as to their action on the isolated artery. Some of these filtrates are active in their effect, and their activity can in some instances be shown, by chemical analysis, to be due to histamine and tyramine hydrochloride, but in many

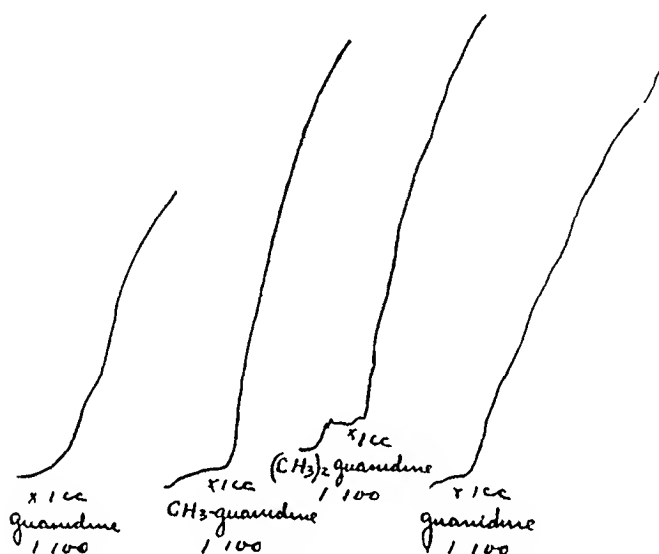


Fig 4—Arterial constriction in vitro due to guanidine, methyl and dimethyl guanidine

other cases the active substance is chemically not identified as yet. A discussion of these studies forms the subject matter of the next article in the series.<sup>9</sup>

<sup>9</sup> Koessler, K. K., Lewis, J. H., and Walker, J. A. Pharmacodynamic Actions of Bacterial Poisons, *Arch Int Med* **39** 188, 1927

# PHARMACODYNAMIC ACTIONS OF BACTERIAL POISONS<sup>1</sup>

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Probably no expression is more frequently used by the clinician and pathologic physiologists to describe certain phenomena during acute and chronic diseases due to bacterial infection than the term "toxemia" or "the toxic action of the micro-organism." Such expressions denote our general tacit agreement that the processes by which pathogenic micro-organisms cause disease consist in the last instance in the chemical action of such poisons on certain organs or organ systems. Yet our real knowledge regarding such action is disproportional to the frequency of the usage of the word toxemia, and this statement holds true nearly as much for the few specific secretory products of the bacteria the true toxins in the immunologic sense of the word as for the unspecific poisons that are formed by the interaction of micro-organisms and tissue cells.

During the last ten years our group of workers in the Otho S. A. Sprague Memorial Institute has concentrated its efforts on one phase of this problem, which was concerned with the chemical study of certain poisons which are formed when micro-organisms grow in a medium containing protein and amino-acids. Quantitative chemical methods were devised that permitted the isolation and determination of these poisonous substances, which are for the most part, chemically well characterized amines. It could be shown that micro-organisms which form histamine or tyramine are normal inhabitants of the human intestinal tract, and the presence of these toxic amines in the normal intestinal content was proved by actual chemical isolation. This work further proved that the catabolism of amino-acids in the intestinal tract proceeds normally not only by deamination, but also by decarboxylation. But more recent investigation showed that this faculty of decarboxylation leading to amine production is not restricted to intestinal bacteria. The mixture of common pyogenic micro-organisms contained in the bronchial secretion, in sputum, in various foci of infection such as the tonsils and in inflammatory exudates, such as empyema fluids, is able to form large quantities of these poisonous amines, such as histamine and tyramine, in vitro.

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<sup>1</sup> From the Otho S. A. Sprague Memorial Institute and the department of pathology, University of Chicago.

The object of the study reported here was not to determine the production and mode of action of the chemically well defined crystalline substances like histamine and tyramine, but to follow up the evidence obtained early in this work that other poisons, as yet chemically undefined, are formed by bacteria under our experimental conditions—poisons which might have a definite pharmacologic activity

# PROCEDURE

The micro-organisms were all grown in 200 cc of a peptone-blood broth, which contained 1 per cent peptone, 2 per cent glycerine, 5 per cent whole sheep blood, and 0.1 per cent histidine or tyrosine. This medium is inoculated with a single strain of bacteria or with the natural mixture of micro-organisms contained in sputum or other body fluids. After an incubation period of two weeks, 25 cc of the culture is filtered through a Berkefeld filter and set aside in sterile tubes for  $pH$  determination and pharmacologic tests. The remaining liquid is heated on the water bath to kill the bacteria and coagulate the proteins.

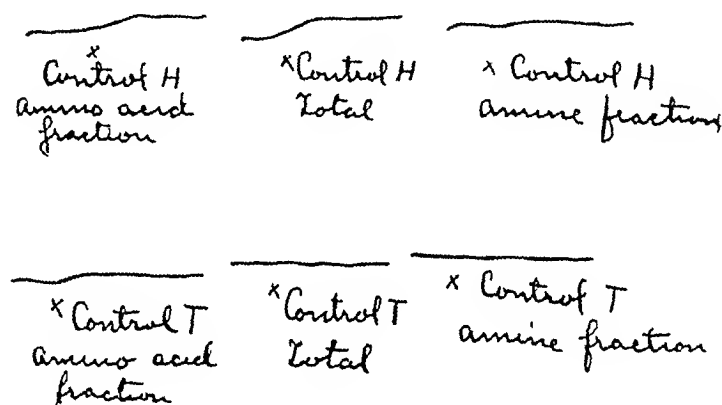


Fig 1—Control tests. Absence of vasoconstrictor effect of the uninoculated medium fractioned according to the usual procedure.

Complete coagulation can sometimes be obtained only after adding a few drops of glacial acetic acid. The mixture is then filtered and the filtrate evaporated on the water bath in a glass dish. The residue is transferred to a graduated cylinder and diluted exactly to 25 cc. When this filtrate could not be analyzed immediately, it was preserved by adding 0.5 cc of concentrated sulphuric acid. The acid has no effect either on the chemical determinations or on the pharmacologic activity after proper neutralizing. Ten cubic centimeters of this liquid is then treated with 3 Gm of sodium hydroxide and extracted six times with amyl alcohol to remove amines. The amyl alcohol fraction is extracted with sulphuric acid. The acid is neutralized with sodium hydroxide and evaporated to dryness on the water bath. The residue is dissolved in water and diluted to 25 cc. The residue remaining after extraction with amyl alcohol is treated with 7 cc of 37 per cent hydrochloric acid solution, evaporated to dryness, dissolved in water and diluted to 25 cc.

By these manipulations the original blood broth culture is divided into four fractions: (1) filtrate filtered through a Berkefeld, but not chemically treated, (2) the concentrated filtrate obtained after removal of the proteins, (3) the amine fraction, which is soluble in amyl alcohol, and (4) the amino-acid fraction, which remains after extraction with amyl alcohol.

The amine fraction, which contains all the amines, was used for the chemical determination of these substances. This and the other fractions after exact neutralization were used in various ways to assay their pharmacologic activity.

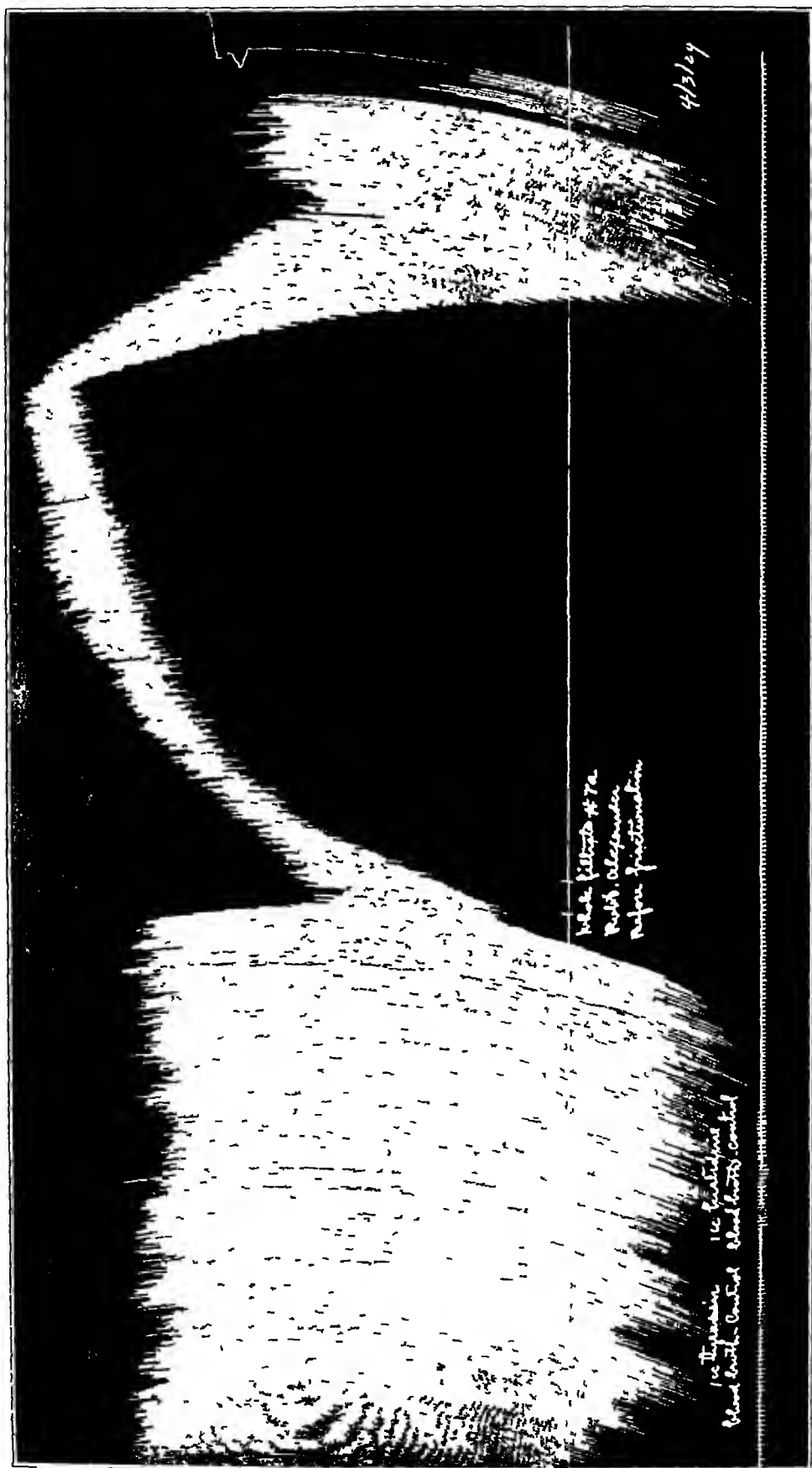


Fig 2 -A, control experiment with tyrosine and histidine glycerol blood broth medium without inoculation, B, whole filtrate from a histidine glycerol blood broth medium that had been inoculated with sputum 7 R A, showing a marked broncholar spasm

The pharmacologic tests were based on the well-known action of amines, typified in histamine and tyramine on smooth muscle tissue. A method which utilizes the smooth muscle of arteries and another one which depends on the reaction of bronchial musculature, both of which are described in the preceding articles, were used as routine procedures in testing these fractions.

### CONTROLS

The methods were well controlled in that the tests were carried out with the Berkefeld filtrate from the standard uninoculated blood-glycerol broth containing histidine or tyrosine. These sterile mediums were fractionated as described above for the cultures. The results obtained with these control tests were uniformly negative (figs 1 and 2). Further controls were obtained throughout the routine testing of the bacterial filtrates, in that numerous filtrates gave negative results.

In several hundred experiments on arteries and bronchi the amino-acid fraction proved to be free from physiologic activity as to vasoconstrictor and broncho-spastic action. The physiologic activity, if present, resides in the Berkefeld filtrate, the total concentrated filtrate and the amine fraction. Since the unheated Berkefeld filtrate showed the same behavior as it did after removal of the proteins, through acetic acid and heat coagulation, pharmacologic tests were subsequently restricted to the total concentrated filtrate, the amine fraction and the amino-acid fraction. The physiologic activity of the amine fraction always corresponds qualitatively to that of the total filtrate, but varies in intensity. Equal amounts of the amine fraction are usually more active than the total filtrates.

In studies previously made on the production of proteinogenous amines,<sup>1</sup> especially histamine and tyramine, by intestinal micro-organisms, isolated specific strains of bacteria were originally used, but so many of these proved to be negative as regards decarboxylation of the amino-acid, and the resulting formation of the corresponding amine, that it was decided to work with the natural mixture of micro-organisms contained in human feces. In this way it could be shown that the intestinal content of man contains, in about 70 per cent of all cases examined, organisms that are able to form histamine or tyramine. Pure strains that were able to convert the amino-acids into the corresponding amines were then isolated from some of these stools. This method of using a naturally occurring mixture of micro-organisms shortened our procedure and gave valuable preliminary information. It was therefore adopted in the present study of the amine production by organism of the respiratory tract.

The mediums were first inoculated with the mixture of bacteria occurring in the expectorated sputum. A small amount of freshly obtained sputum was introduced into a test tube containing 5 cc of sterile broth, which was vigorously rotated between the hands to wash off surface contamination. Then three loopfuls of this mixture were transferred into another tube containing 5 cc of broth, and after vigorous shaking to obtain a good suspension, three loopfuls were transferred to two flasks of medium, one containing tyrosine and one histidine. After two weeks' incubation the cultures were fractionated as described above and the fractions studied chemically and pharmacologically.

### RESULTS

It soon became evident, in contradistinction to the results obtained with intestinal organisms, that in the majority of instances both tyramine and histamine were completely absent, yet the filtrates possessed very

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1 Literature references are given in the preceding articles. Lewis, J. H., and Koessler, K. K. Demonstration of Arterial Constriction in Vitro. A New Method, *Arch. Int. Med.* **39** 182, 1927. Koessler, K. K., and Lewis, J. H. The Determination of Bronchospasm in the Guinea-Pig. Applications of the Method, *ibid.* **39** 163, 1927.

powerful pharmacologic amine activity, as evidenced by the action of the whole filtrate and the amine fraction on the bronchial and arterial musculature

This observation was made on the first sputum from a pneumonia patient examined. It had been shown in our studies on the formation of proteinogenous amines by decarboxylation that the production of these poisonous substances was invariably associated with a change in reaction of the medium toward the acid side. Only in a distinctly acid medium are histamine and tyramine formed. The  $p_H$  of the first pneumonia sputum examined (Thomas Healy), after inoculation and fourteen days' incubation in histidine blood-glycerine-broth, was 7.8. This in itself was strongly suggestive evidence that histamine or tyramine had not been formed, which was proved to be the case by chemical analysis. The alkaline reaction of the medium does not preclude the formation of substances of amine structure, it would suggest however that they are not formed by decarboxylation (triamines?). In 0.5 cc amounts of the total test solution and amine fractions a most intensive bronchoconstriction and vasoconstriction were obtained. The amino-acid fraction, on the other hand, was pharmacologically completely inert, showing that the active principle is completely soluble in amyl alcohol another item of evidence as to its amine nature (fig. 3).

The inoculation of a tyrosine blood broth medium with a sample of the same sputum made on the same day did not yield a trace of tyramine, neither was any pharmacologic action obtained with any of the three fractions.

The behavior of a different sample of sputum from another patient with pneumonia (Ben Green) was entirely at variance from that of the first one. In the histidine medium, 62 per cent of the histidine was converted into histamine, and because of this amine 0.5 cc of the amine fraction given intravenously immediately killed with bronchospasm a guinea-pig of 600 Gm (fig. 4). An intense arterial constriction was obtained with the total and amine fractions. The same sputum when inoculated into the tyrosine medium yielded 45.6 per cent tyramine. The fractions of this culture also produced a fatal bronchospasm and an intense arteriospasm. The action on the bronchi in this instance however, cannot be attributed entirely to tyramine, for this substance exerts such an action only in a much higher dose than was present in 1 cc of the amine fraction. The arterial constriction could have been due to the tyramine.

Sputum sample 4 was obtained from patient M, suffering from a severe bronchitis and tonsillitis, in the histidine medium no decarboxylation ( $p_H$  7.6) occurred and not a trace of histamine was formed. But the total test solution and amine fraction contained a bronchospastic poison of such intensity that 1 cc killed a 700 Gm guinea-pig in apnea.

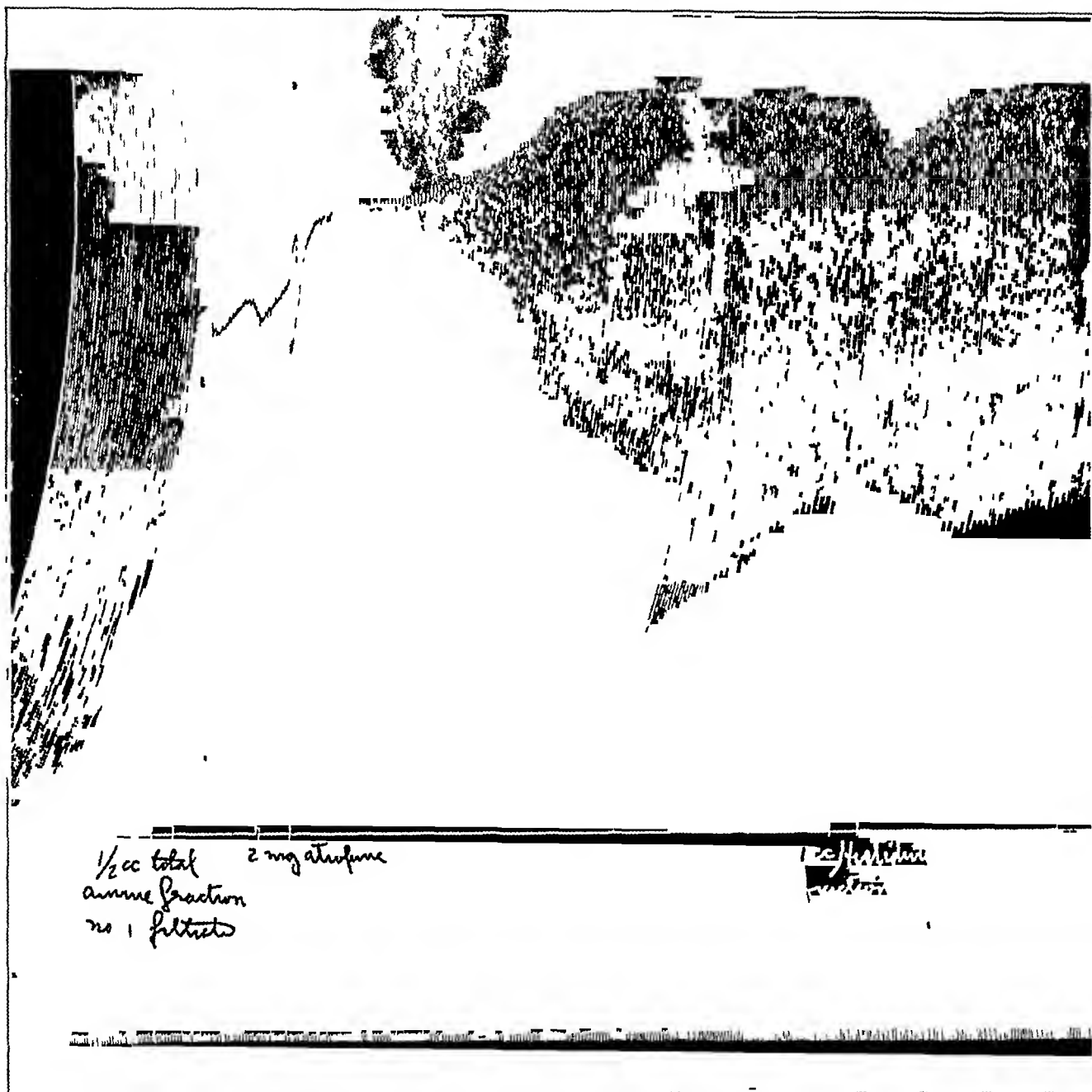


Fig 3—Amine fraction of sputum 1 T H histamine and tyramine were absent, the bronchiolar spasm was caused by some substance of unknown constitution, possibly an amine

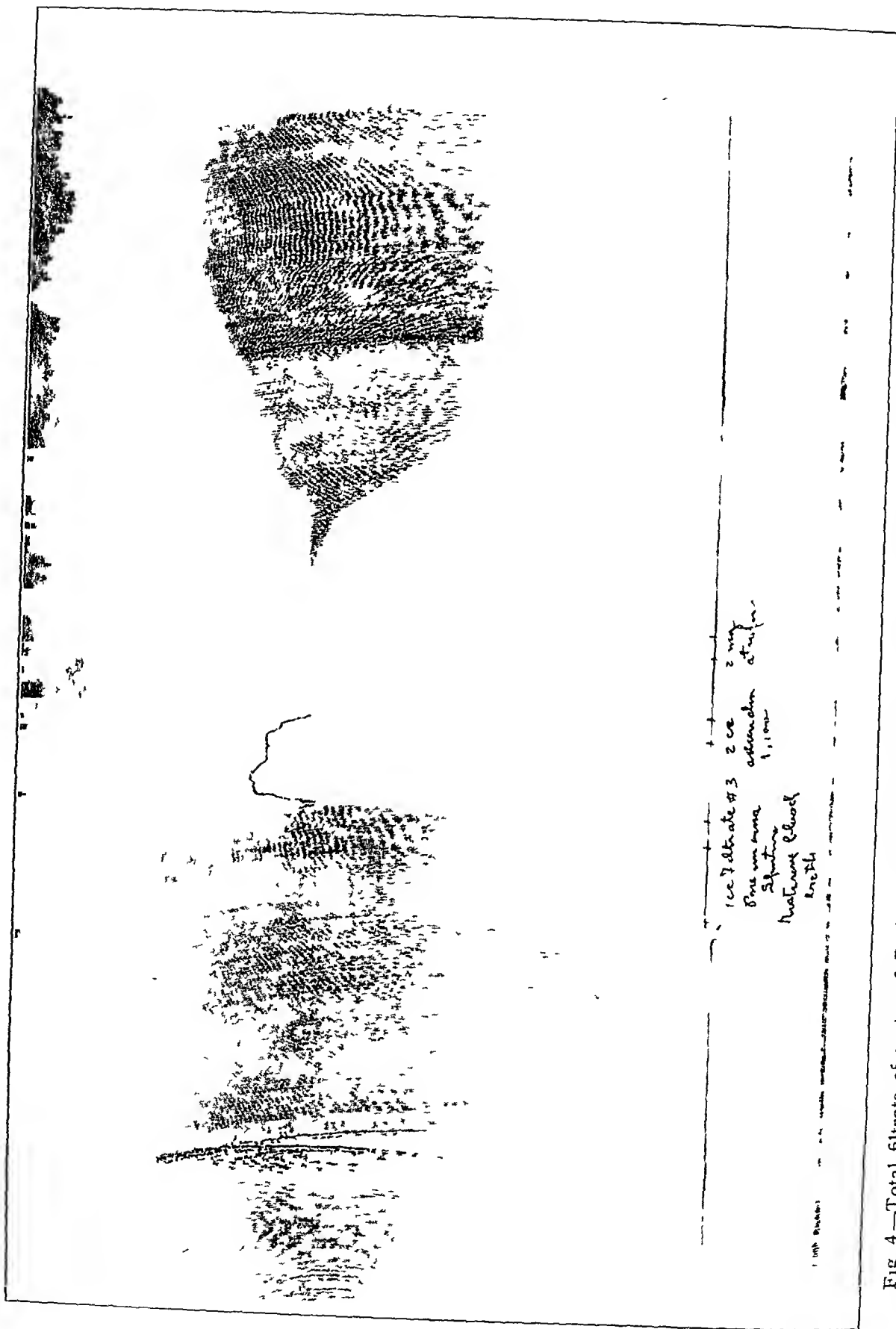


Fig 4—Total filtrate of sputum 3 P J The fatal broncholar spasm was due to the histamine which had been produced by this mixture of micro-organisms

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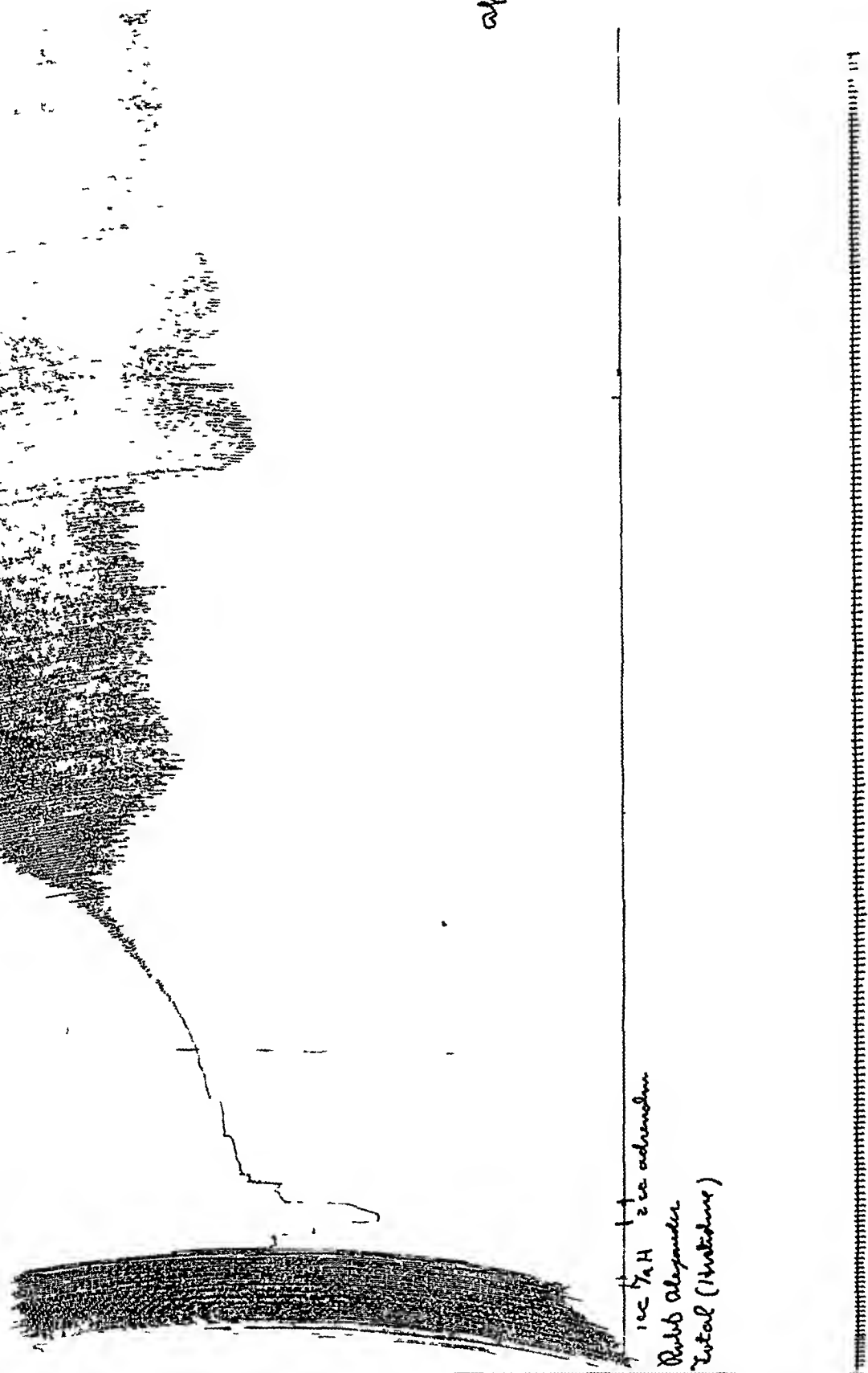


Fig 5—Total filtrate of sputum 7 R A The broncholar spasm was due to poison of unknown constitution, histamine was absent

(fig 5), also, a marked arterial constriction was obtained with the same fractions (fig 6). The amino-acid fraction again proved completely without pharmacodynamic effect. The sputum inoculated on the same day and in the same quantity into the tyrosine medium led to the formation of 125 mg of tyramine, which represents 60.2 per cent conversion. The  $p_H$  of the medium after fourteen days' incubation was 5.6. An intense degree of arterial and bronchial spasm was produced in the pharmacologic tests.

In sputum 5, taken from patient P. S., suffering from lobar pneumonia, no histamine was formed after two weeks' incubation of the

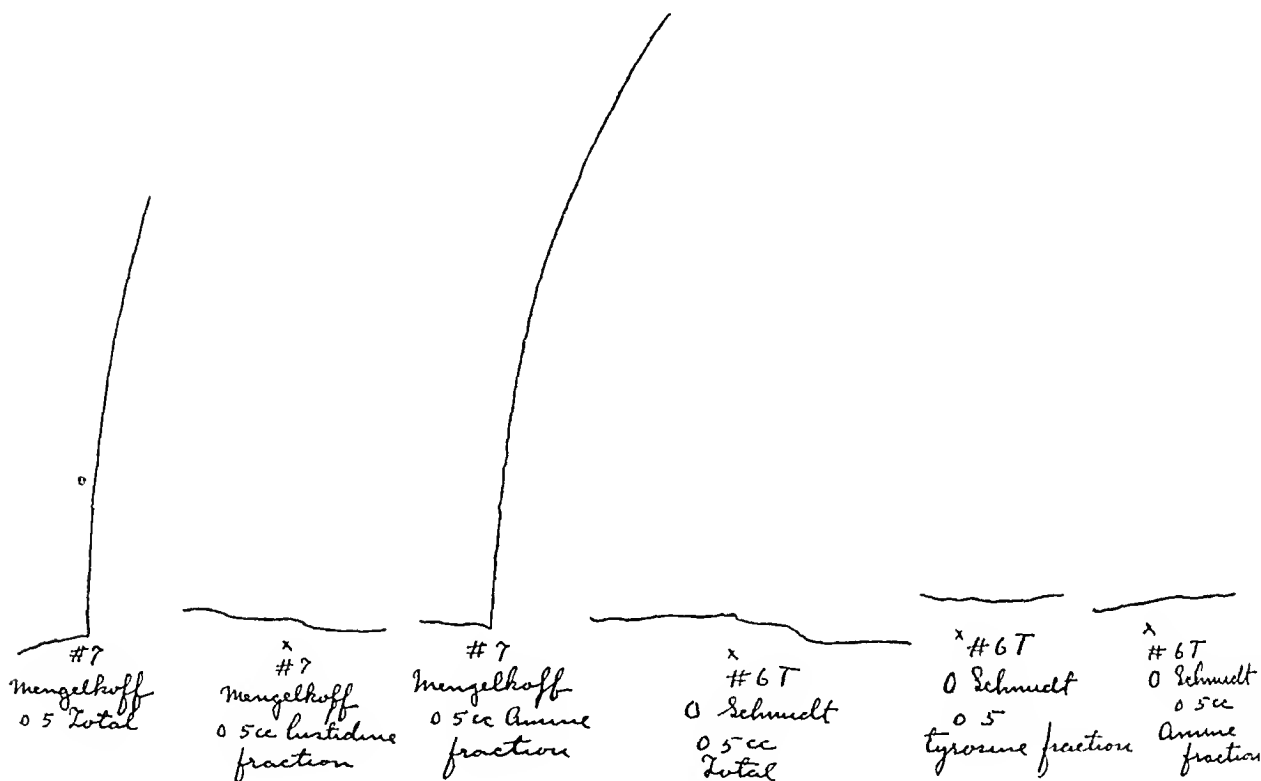


Fig 6—Arterial constriction obtained with fractions from medium that had been inoculated with sputum 4 M. K. The absence of contraction with the amino-acid fraction should be noted. Pus sample 6 O. S. did not contain arteriospastic substances.

inoculated histidine-blood-broth-glycerine medium. The pharmacologic test showed a pronounced bronchial and vascular constriction. In the tyrosine medium decarboxylation of tyrosine with 98 per cent conversion into tyramine took place. Both pharmacologic tests proved strongly positive (fig 7).

The pus from two postpneumonic empyemas containing many pneumococci, proved entirely negative, while the incubation of the purulent sputum of a lung abscess led to the formation of a poison which gave intense bronchospasm, but was without effect on the arteries. This

selective action of the poison, while not the rule, has been encountered several times. Most frequently the poison which causes bronchiolar constriction leads also to vascular constriction *in vitro*. In some instances, however, the activity is restricted to only one of the smooth muscle fiber systems, intense vasoconstriction may result from a poison

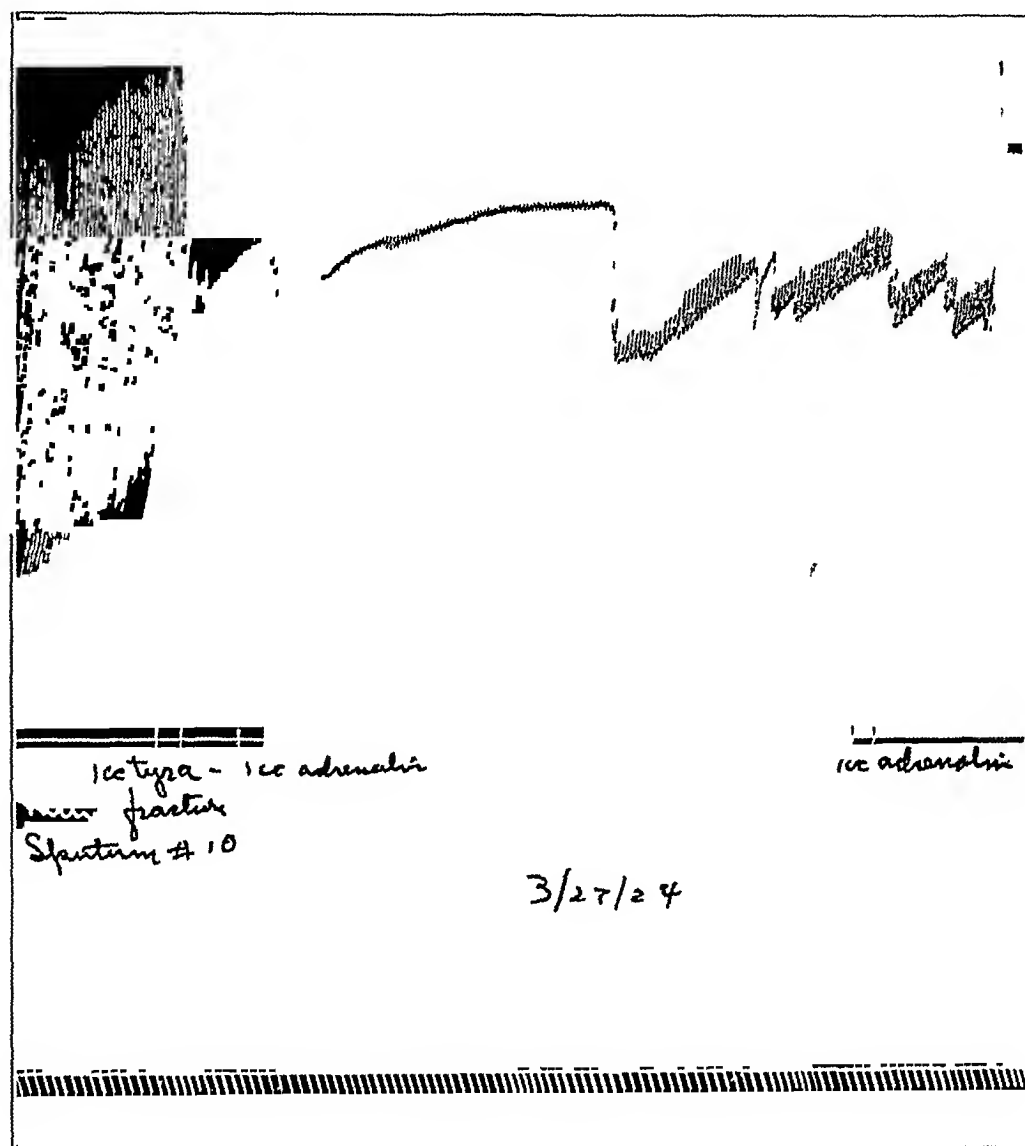


Fig 7—Amine fraction of sputum 10 S S. This fraction contained tyramine, but the bronchiolar spasm obtained cannot have been caused by this amine.

contained in the amine fraction, which is without effect on the pulmonary excursions and the bronchi (fig 8).

In this manner the sputum of many patients suffering from various respiratory diseases was inoculated into the blood-glycerin broth containing histidine and tyramine, and the fractions obtained examined for physiologic activity. In addition, empyema fluid and pus from lung abscesses were treated in a similar manner. It was found that there

were by far many more instances in which not a trace of histamine or tyramine had been formed than instances in which these amines could have led to the production of histamine derived from the histamine con- be demonstrated Yet in the absence of any one of these two amines we frequently—in about 70 per cent of all cases examined—found substances which acted distinctly on the bronchi and the arteries

Table 1 contains a list of the sputums, empyema fluids and other five led to the production of histamine derived from the histidine con-

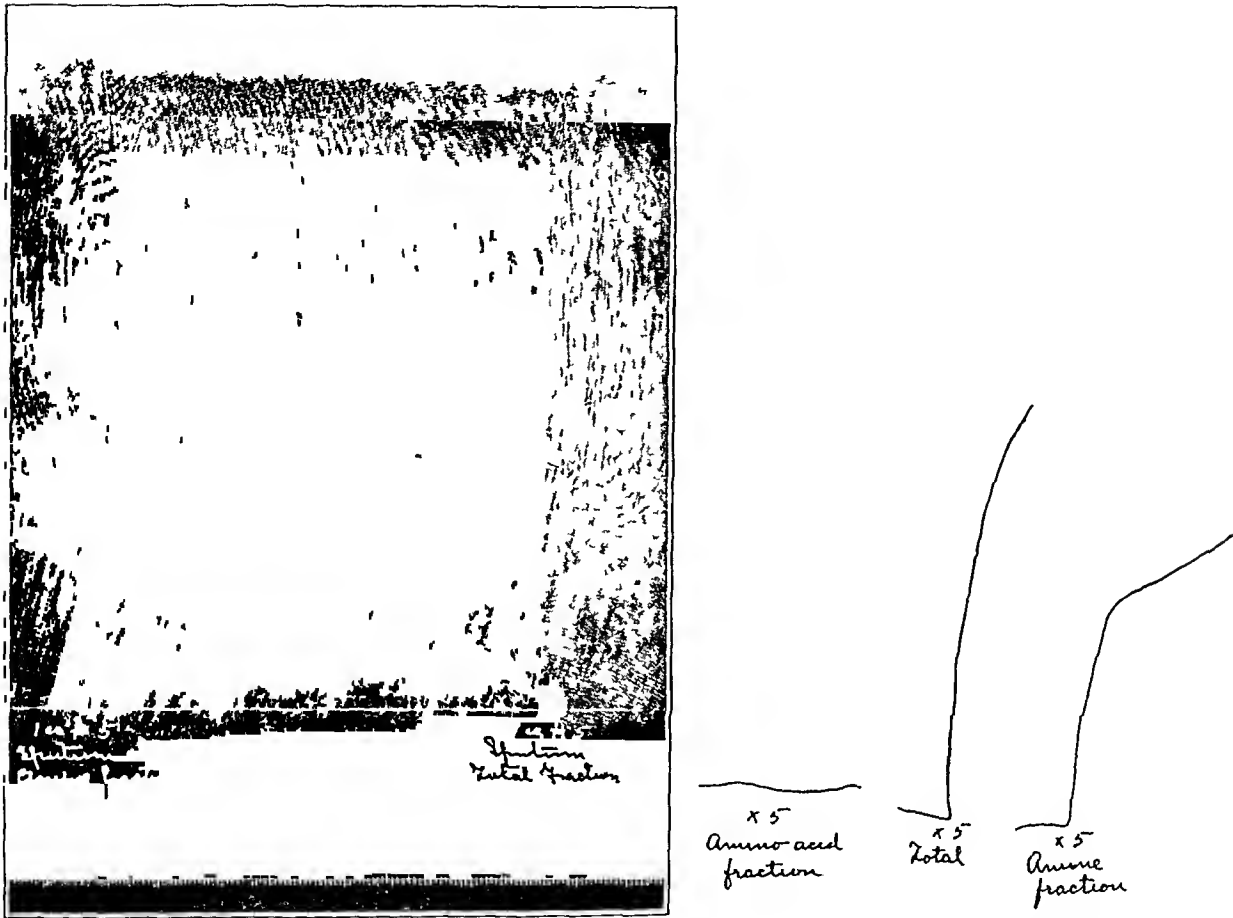


Fig 8—Fractions from sputum 5 P S Bronchospastic substances were absent and arteriospastic substances were present The absence of constrictor substances in the amino-acid fraction should be noted

tained in the medium Five produced tyramine by decarboxylation of the tyrosine added to the medium

Of the thirty-seven specimens, five produced histamine, five produced tyramine, fifteen formed bronchospastic substances which were neither histamine nor tyramine, eighteen formed arteriospastic substances, neither histamine nor tyramine, one produced both histamine and tyramine, and nineteen produced both bronchospastic and vasoconstrictor substances

TABLE 1—*Production of Bronchospastic and Arteriospastic Substances by the Mixture of Micro-Organisms Contained in Sputums and in Purulent Exudates*

Case	Sputum from Case	Diagnosis	Reaction After Incubation		Histidine Re- covered per Cent	Histidine Con- verted into Histamine per Cent	Tyrosine Con- verted into Tyramine per Cent	Bron- cho- spasm	Arterio- spasm
			Blood Broth Me- dium plus Histidine per Cent	Blood Broth Me- dium plus Tyrosine per Cent					
1 2	1 T H	Pneumonia	78	66	10	None	None	1+	4+
3 4	2 B G	Pneumonia	76	78	75	62	None	1+	4+
5 6	3 P J	Empyema	78	78	53	None	Present	None	1+
7 8	4 M K	Bronchitis	76	76	90	None	Present	61 75	1+
9 10	5 P S	Pneumonia	72	72	50	None	None	98 0	4+
11 12	7 R A	Pulmonary tuberculosis	73	71	35	None	None	72 0	1+
13 14	9 Os	Lung abscess	76	80	50	None	None	None	None
15 16	10 S S	Bronchiectasis	71	72	70	None	None	None	3+
17 18	11 C D	Bronchitis	64	71	30	None	75	None	1+
19 20	12 R G	Pneumonia	80	82	50	None	Present	None	4+
21 22	13 S U	Pulmonary tuberculosis	72	72	10	None	Present	None	1+
23 24	14 S	Bronchiectasis	78	77	110	31	None	None	1+
25 26 27	15 C C	Asthma	76	76	92	None	Present	None	1+
28 29 30	16 T J W	Pneumonia	78	60	40	None	Present	None	1+
31 32 33	17 C S	Pneumonia	54	60	110	None	Present	None	1+
34 35 36	18 M L	Pneumonia	76	62	15	15	Present	None	1+
37 38	22 W P	Bronchiectasis	76	66	65	None	None	None	1+
39 40	23 J C	Bronchiectasis	66	73	95	33 5	Present	None	1+
41 42	24 A L	Pneumonia	64	71	15	None	Present	None	None
43 44	25 R S	Bronchiectasis	76	64	100	None	None	None	None
45 46	26 C D	Pneumonia	76	60	110	None	None	None	None
47 48	27 T S	Pneumonia	76	54	15	None	None	None	None
49 50	28 O W	Pneumonia	78	71	81	None	None	None	3+
51 52	29 W D	Pneumonia	76	76	23	None	None	None	None
53 54	30 G L	Tuberculosis	71	62	73	None	Present	None	1+
55 56	31 G B	Pneumonia	76	52	87	None	Present	None	2+
57 58	32 M J	Pulmonary tuberculosis	73	66	28	None	Present	None	4+

TABLE 1—Production of Bronchospastic and Arteriospastic Substances by the Mixture of Micro-Organisms Contained in Sputums and in Purulent Exudates—Continued

Case	Sputum from Case	Diagnosis	Reaction After Incubation						Broncho-spasm	Arterio-spasm
			Blood Broth		Histidine converted per cent	Tyrosine converted per cent	Tyrosine converted per cent			
			Blood Broth	Ma. d. 10						
								Ma. d. 10		
50	33 P H	Pulmonary tuberculosis	1	7	0	None	None	None	None	
51	34	Pneumonia	1	1	2	None	None	None	1-	
52	35	Bronchitis	1	0	0	None	None	4-	4-	
53	36	Pneumonia	1	1	0	None	None	None	None	
54	37	Influenza	1	0	0	None	None	None	None	
55	38 B V	Pneumonia	1	7	0	None	None	4-	4-	
56	39 C G	Bronchial abscess	1	0	0	None	None	4-	0-	
Per Samples										
1	40 S	Empyema	1	0	0	None	None	None	None	
2	41	Empyema	1	7	0	None	None	None	None	
3	42 B F	Empyema	1	7	0	None	None	None	None	
4	43	Maxillary sinus	1	0	0	None	None	4-	4-	
5	44	Maxillary sinus	1	0	0	None	None	4-	4-	

Thus, in all, twenty (54 per cent) produced bronchospastic substances and twenty-six (70 per cent) formed arteriospastic substances.

While the study of the pharmacodynamic action of such mixtures of micro-organisms as are contained in pathologic bronchial secretions and in other inflammatory exudates is of great interest, it is evident that the results obtained at once invited the extension of this study to the metabolic products formed by isolated pure strains of micro-organisms to ascertain which ones were responsible for the production of the poisonous substances. Therefore, the pathologic fluids that produced active filtrates were cultured and as many organisms isolated in pure culture as possible. These pure strains were then inoculated, in counted numbers into the standard mediums. From then on the procedure was the same as with the whole mixture.

Sputum 7 was studied first in this way. The specimen came from a patient who had an extensive tuberculosis of both lungs with small cavities. A secondary infection was associated with the tuberculous infection and a gram stain of the sputum showed many gram-positive and gram-negative organisms.

The total sputum in the histidine as well as tyrosine blood broth medium had produced bronchospastic and arterioconstrictor poisons the

first of such intensity that the guinea-pig was killed in both instances on intravenous injection of 1 cc of the total concentrated fraction. This filtrate contained not a trace of histamine, but 72 per cent conversion of tyrosine to tyramine had taken place. In all, eleven organisms were isolated from his sputum. One, designated as organism 3, was a small gram-positive streptococcus. In the histidine-glycerin-blood broth this organism formed a poison, not histamine, which caused a marked

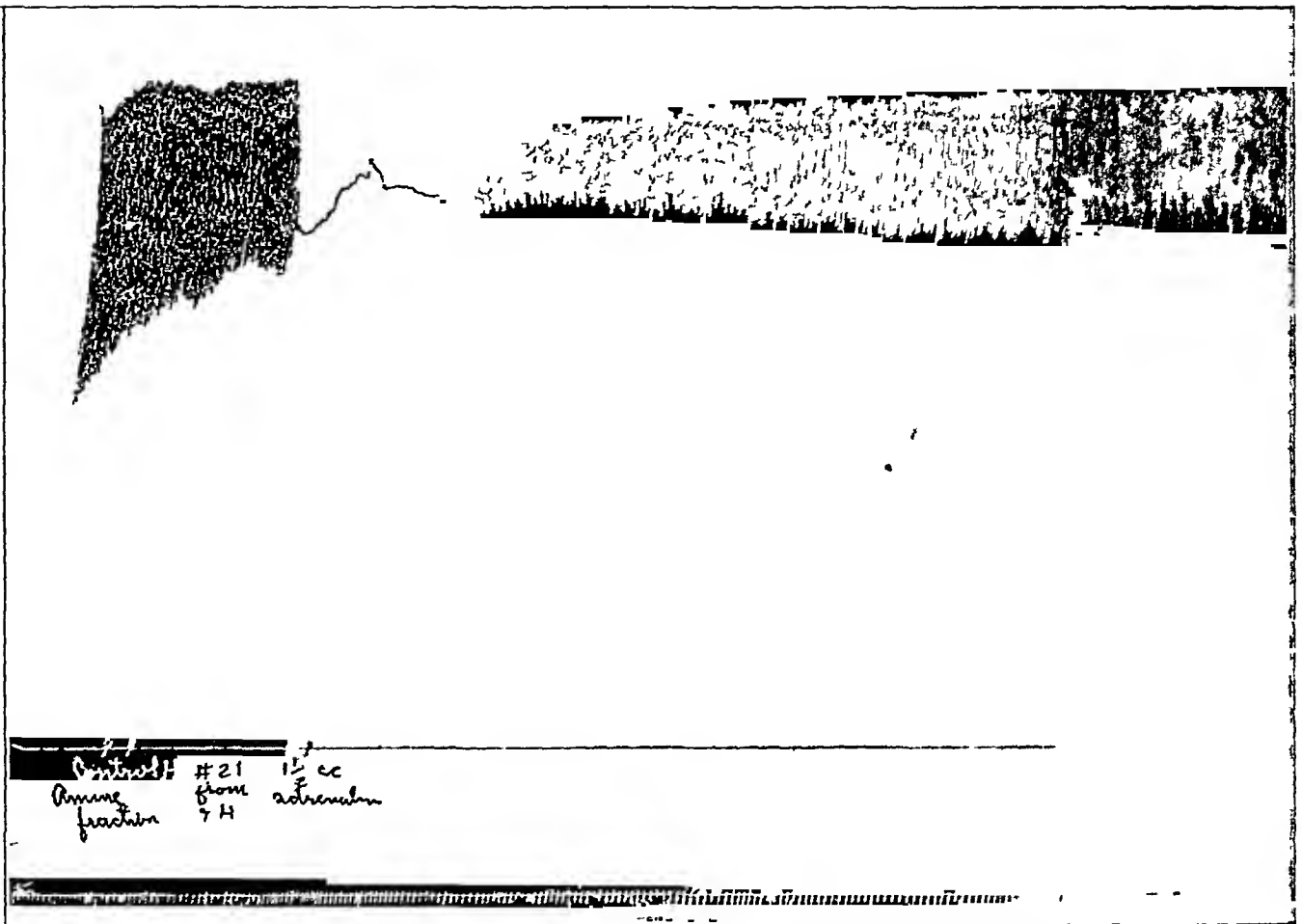


Fig 9—Organism 21 isolated from sputum 7 R A. The bronchospasm was due to histamine.

arterial constriction in vitro, but no bronchiolar contraction in the living pithed guinea-pig. The same coccus grown for the same period (fourteen days) in the tyrosine medium formed a poison, not tyramine, which produced a marked bronchoconstriction and arterioconstriction.

Another organism, 21, isolated from this sputum, was a gram-negative bacillus resembling *Bacillus subtilis* in certain morphologic and chemical characteristics. It formed an unidentified poison which caused intense bronchoconstriction (fig 9) as well as vasoconstriction. A stock culture as well as a freshly isolated typical strain of *B. subtilis* caused

only arterial constriction, but was without effect on the pulmonary excursions

Organism 11, a gram-negative bacillus caused marked bronchiolar spasm (fig 10) but was without effect on the arterial musculature in vitro Organism 42, a long gram-negative bacillus, yielded fractions in the culture mediums which were without effect in pharmacologic tests

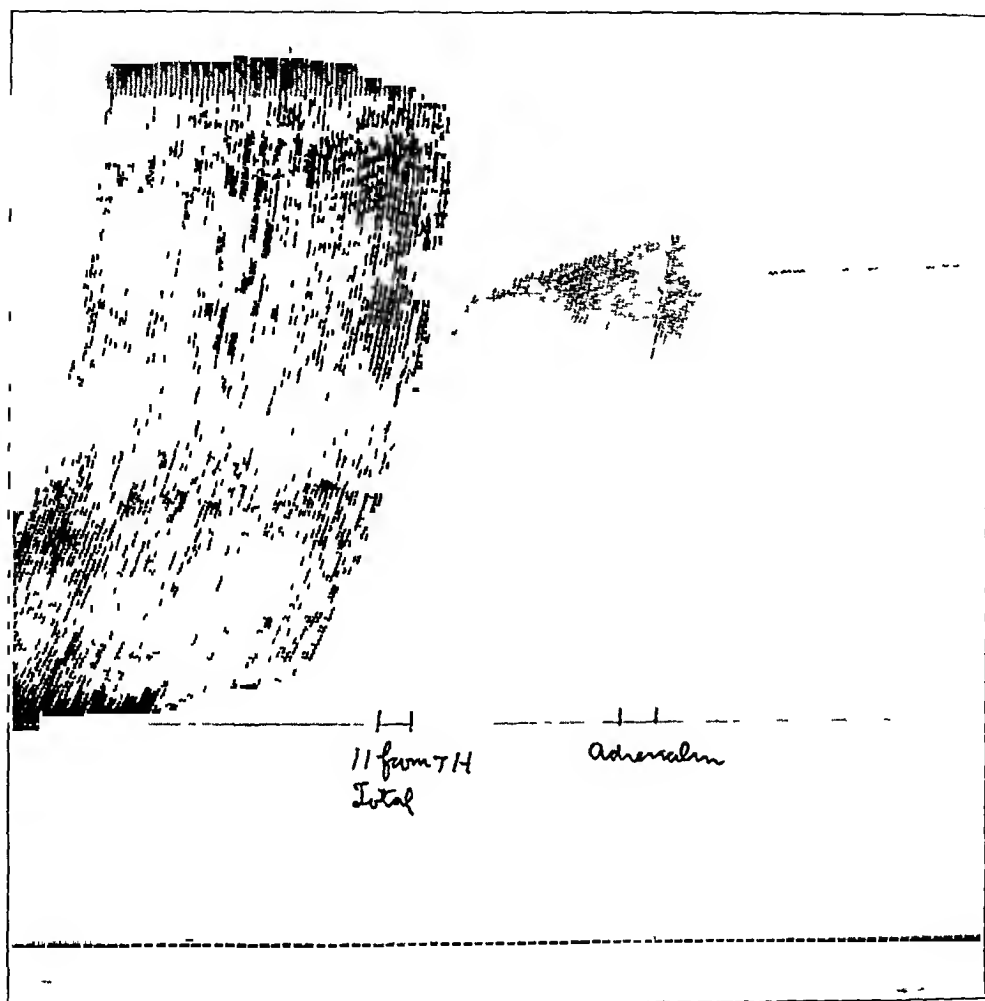


Fig 10—Organism 11 from sputum 7 R A The bronchospasm was due to substances of unknown chemical constitution, histamine was absent

A gram-positive yeast, organism 38, formed no active poison Organism 9, a gram-positive coccus, different in morphologic and cultural characteristics from organism 3, formed, like this coccus, a substance active on the arteries but inactive on the bronchi

Organism 10, another gram-positive coccus, formed 98 per cent tyramine in the tyrosine medium and showed intense arterioconstriction but only weak bronchoconstriction

A specimen of a purulent exudate from a subacute inflammation of a maxillary sinus (patient S Thomas) yielded *Staphylococcus aureus*

and a streptococcus. Both organisms formed a substance in the glycerin-blood broth histidine medium which caused arterial constriction, but which was without effect on lung volume. The results obtained with the purulent exudates of these various sources and the pure strains isolated therefrom are given in table 2.

TABLE 2—*Production of Bronchospastic and Arteriospastic Substances by Pure Strains of Micro-Organisms*

Number of Micro-organism	Source	Classification	Reaction After Incubation		Histidine converted into histamine, per Cent	Tyrosine recovered, per Cent	Tyrosine converted into tyramine, per Cent	Bronchospasm	Arterial Spasm
			Blood Broth Medium Plus Histidine per Cent	Blood Broth Medium Plus Tyrosine per Cent					
1	Sputum 7 R A	Gram negative coccus		5.0		Present	None	None	None
3	Sputum 7 R A	Gram negative coccus		5.0		Present	None	3+	3+
9	Sputum 7 R A	Gram positive coccus		5.0		60	None	None	4+
10	Sputum 7 R A	Gram-positive coccus		5.0			98	1+	4+
3H	Sputum 7 R A	Gram positive coccus	5.2		132	None		None	3+
11H	Sputum 7 R A	Gram negative bacillus	7.2		122	None		4+	None
21H	Sputum 7 R A	Gram positive bacillus	5.6		132	57		4+	4+
21H	Sputum 7 R A	Six months later	7.6		90	None		4+	4+
38H	Sputum 7 R A	Gram positive bacillus and yeast	5.8		140	None		None	None
42H	Sputum 7 R A	Gram negative bacillus	7.8		132	None		None	None
1	Sputum 21 F N	Gram positive coccus	7.0		110	None		None	1+
1	Pus (Thomas)		6.0					None	4+
2	Pus (Thomas)		4.8					None	4+
3.9		B paratyphosus A	5.2			None		4+	4+
339		B paratyphosus A		5.2		Present	None	3+	1+
212		B paratyphosus A	5.2			None		None	4+
212		B paratyphosus A		6.0		Present	None	None	4+
251		B paratyphosus B	5.2			None		None	4+
251		B paratyphosus B		5.0		Present	None	4+	4+
404		B paratyphosus B	6.0			None		None	4+
404		B paratyphosus B		6.4		Present	None	4+	None
Birmore		B typhosus	5.8			None		None	None
Barmore		B typhosus		5.8		Present	None	None	4+
F B		B typhosus	5.0			None		4+	1+
E B		B typhosus		6.2		Present	None	4+	4+
Hopkins		B typhosus	5.4			None		4+	4+
Hopkins		B typhosus		5.6		Present	None	None	None
		Dysentery Shiga	6.0			None		None	4+
		Dysentery Shiga		6.0		Present	None	None	1+
		Dysentery Flexner	7.6			None		None	1+
		Dysentery Flexner		7.6		Present	None	None	1+
C C H		B coli	6.0			31		4+	4+
		B coli		6.6		Present	None	None	None

A number of other pathogenic organisms in pure culture were studied, some of which were recently isolated, while others were stock cultures

All of eight strains of *Bacillus typhosus* and *Bacillus paratyphosus* yielded filtrates that caused intense arterial constriction, but only three of this number produced substances that caused bronchospasm

A study of the colon group, in the stricter sense, emphasizes anew that the production of poisonous substances pharmacologically active is

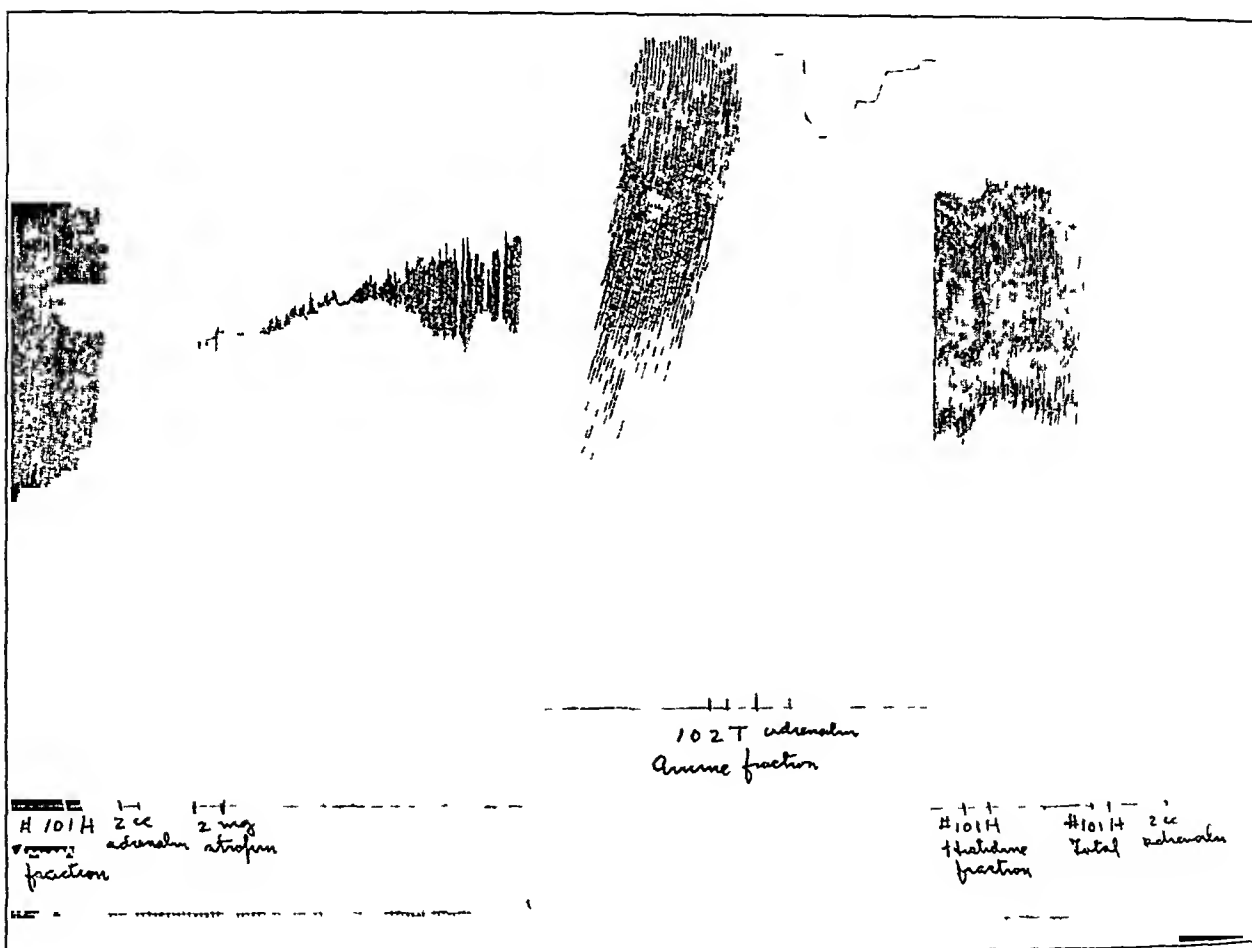


Fig 11 —Bronchospasm obtained with streptococci

associated with certain strains of a bacterial species, which by their other cultural and chemical behavior cannot be distinguished from other strains of the same species. It is a peculiar property with which the bacteriologist and immunologist have been acquainted for years. For example, among the organisms that form a true toxin in the immunologic sense, as the diphtheria, tetanus, dysentery and Welch bacillus, certain strains can be found which do not possess this faculty of forming a toxin, or at least to only a slight degree. Yet these strains differ in no other respect except in their ability to form toxin.

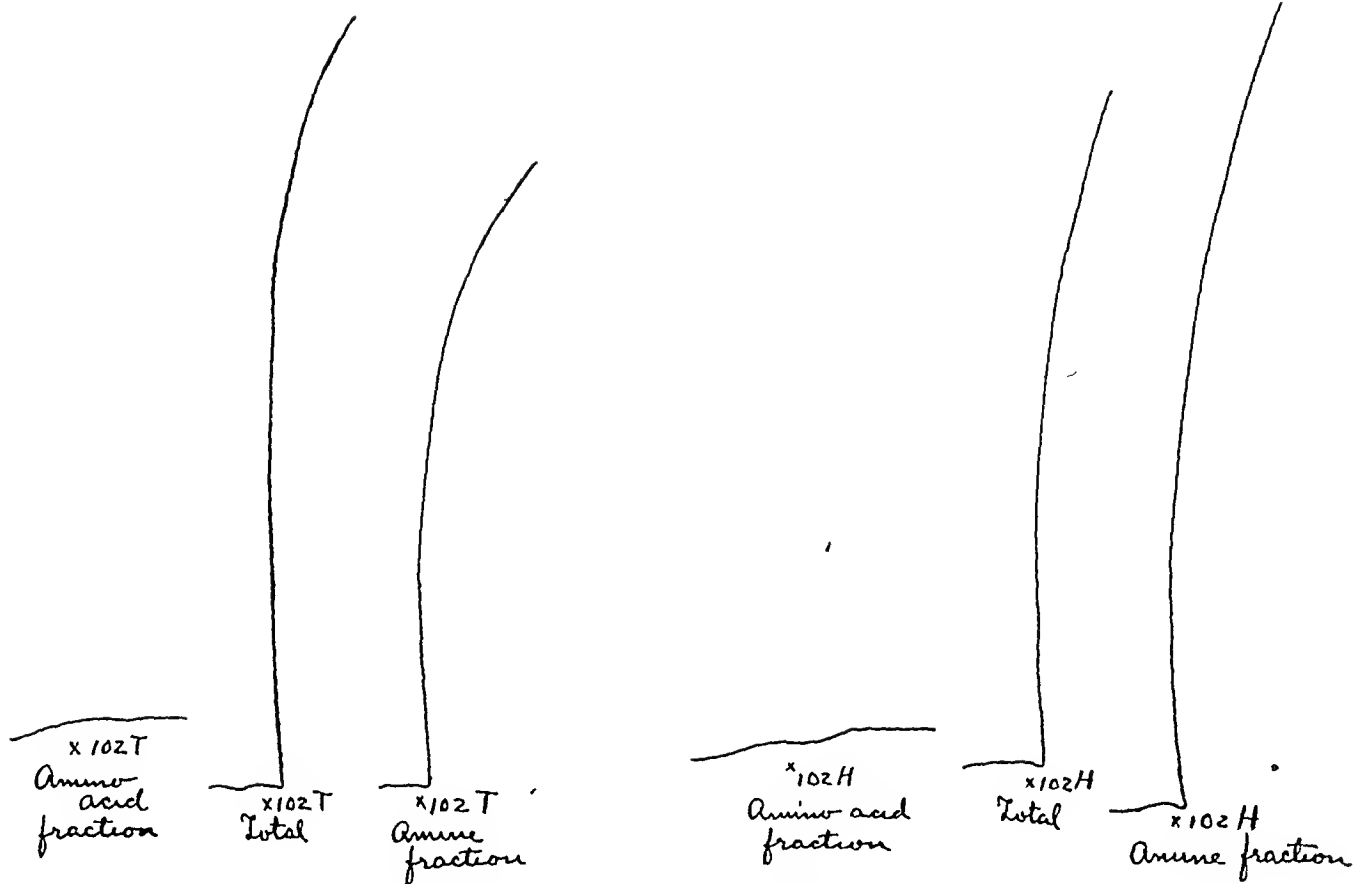


Fig 12—Arterial constriction with hemolytic streptococci

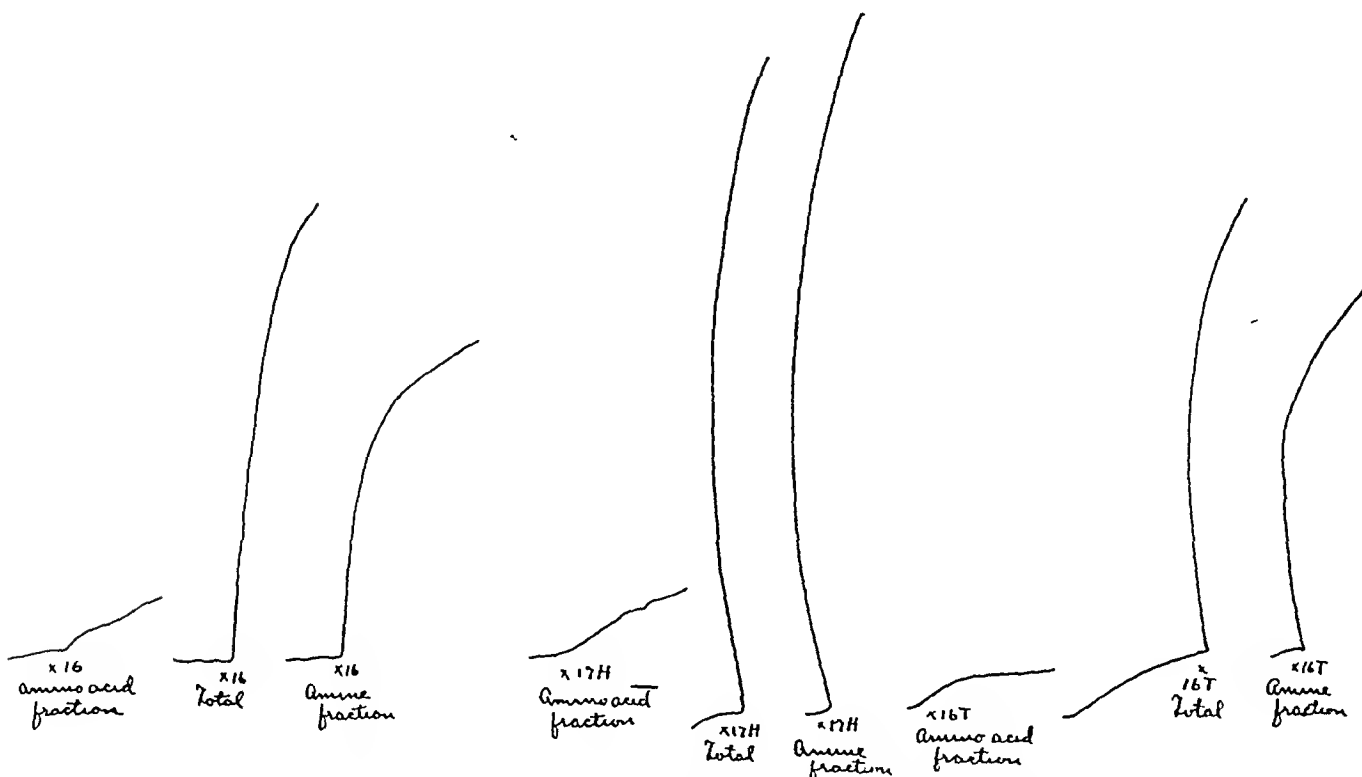


Fig 13—Arterial constriction with filtrates from sputums 16 T J W and 17 C S (two patients with pneumonia) histamine was absent

Fig 14 —Fall in blood pressure obtained with the same fractions that gave arterial constriction in vitro as shown in figure 13

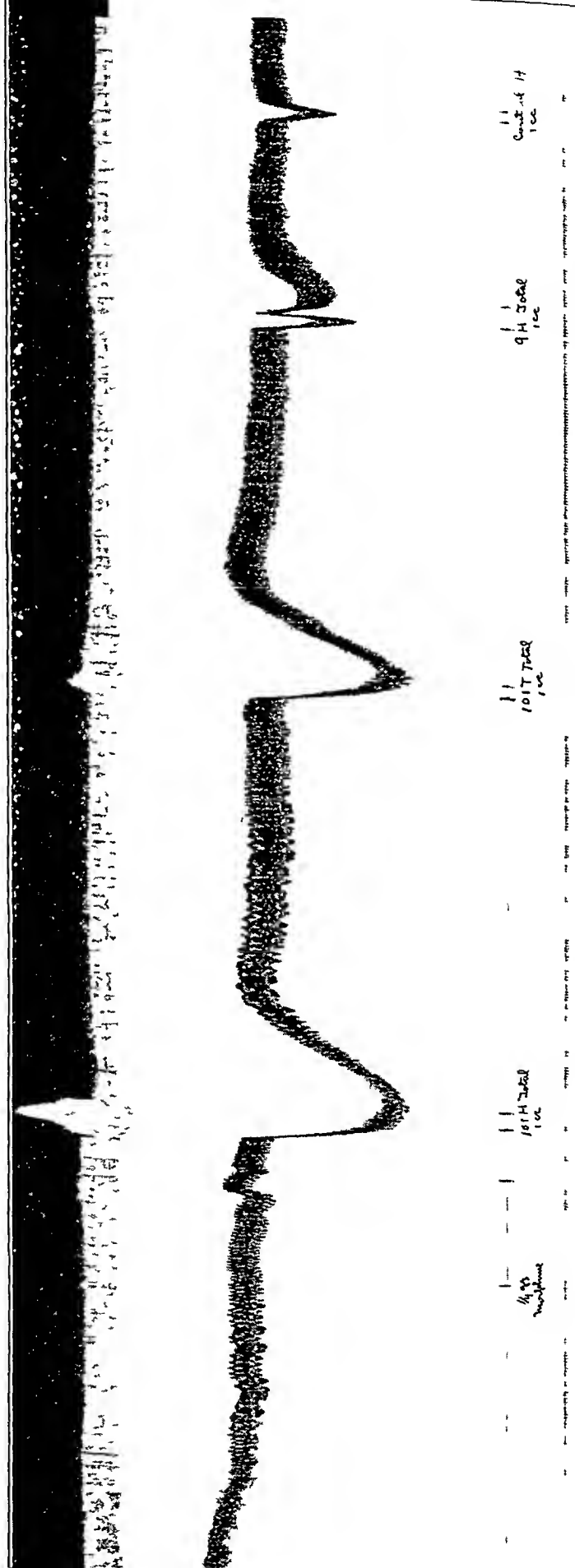


Fig 15 —Fall in blood pressure obtained with filtrate from hemolytic streptococcus which caused arterial constriction in vitro

In our studies on the production of histamine by the colon group, it was found that of seven strains of *Bacillus coli-communior*, three formed histamine, of five strains of *Bacillus coli-communior*, only one formed histamine, of five strains of *Bacillus aerogenes*, one, and of eleven strains of *Bacillus acidilactici*, one. No correlation could be found between the faculty of any group to decarboxylate histidine to histamine and any other chemical characteristic, as, for instance, fermentation of various sugars and starches. The same holds true for the formation of pharmacologically active but unidentified substances by *B. coli* in the glycerin-blood broth histidine and tyrosine mediums. The concentrated filtrate of several strains which formed neither histamine nor tyramine contains in some instances a substance that contracts the smooth muscle fibers of the arteries and bronchi, sometimes both, in some cases only one or the other.

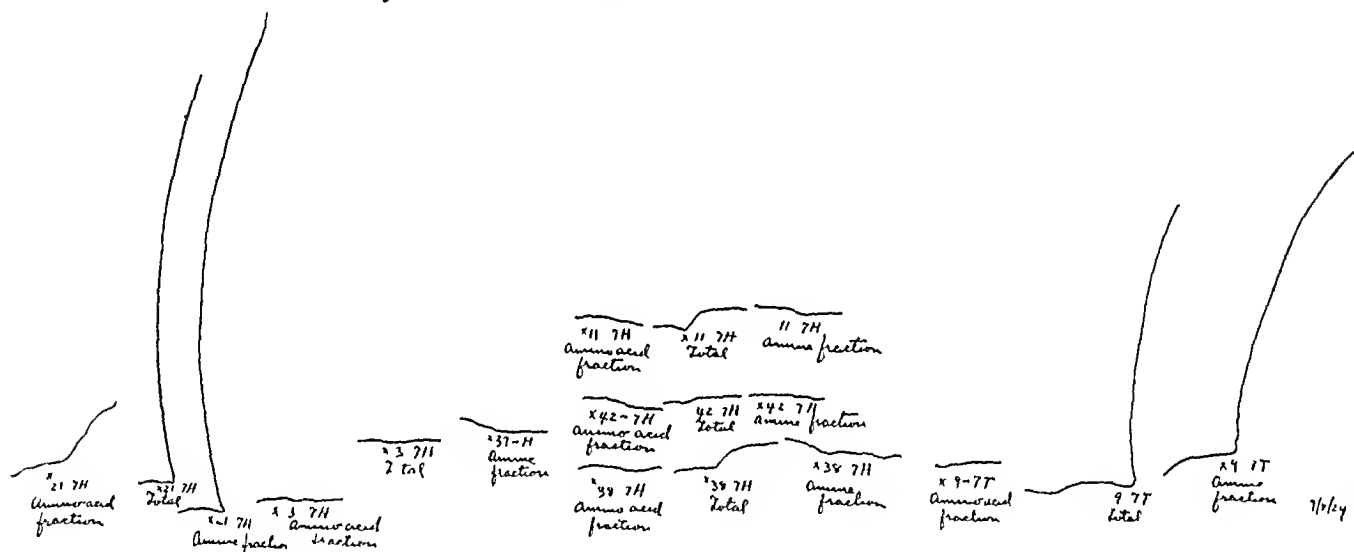


Fig 16—Action on arteries in vitro of filtrates from a number of micro-organisms isolated from sputum 7 R A. Substances produced by organism 9 caused arterial spasm in vitro and a rise in blood pressure in vivo (fig 17)

Thus a strain of *B. coli-communior* designated as C S 2, caused a marked bronchiolar spasm in the pithed guinea-pig and arterial contraction in vitro, while a fraction obtained by the identical chemical procedures from a *B. coli-communior* (designated as S A B) had no physiologic activity on lungs or arteries. Both strains were freshly isolated from human feces.

Another strain of *B. coli* formed a marked bronchospastic poison in the histidine broth, yet not a trace of histamine. The same organism grown in the tyrosine broth did not yield a substance which affected the bronchi.

In the streptococcus group an almost similar behavior is to be observed. Regarding the production of amines of known constitution, we have shown that out of eighteen different strains of streptococci, five

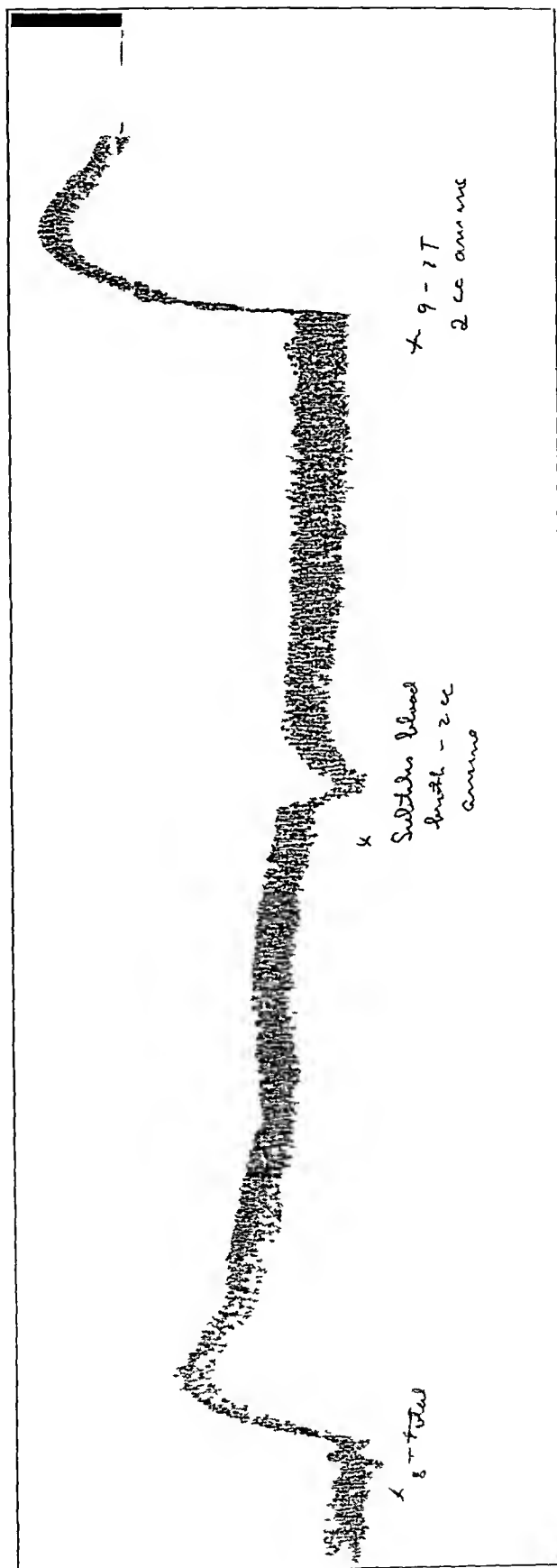


Fig 17 —Epinephrine-like action of substances produced by organism 9 from sputum 7 R A

decarboxylate tyrosine to tyramine. Thirty-five other strains of streptococci were obtained from different diseases by blood cultures, from pus, exudates and focal infections. Of this number, nine yielded a fraction, after cultivation in the broth medium, which was pharmacologically active. Of these nine fractions, four were active on arteries and bronchi, three on arteries alone, and two on bronchi alone (figs 11 and 12).

It is well known that histamine causes a marked fall in systemic blood pressure, yet *in vitro* it produces an intense contraction of the arterial strip. The bacterial poisons, chemically not identified and obtained by fractionation of the bacterial filtrates, showed a similar difference between *in vivo* and *in vitro* action. Thus, the amine fraction and total filtrate from 17 T (a sputum culture from a patient with lobar pneumonia) showed a marked arterial spasm *in vitro* (fig 13), yet the intravenous injection of 2 cc of the filtrate into the rabbit gave a marked fall of systemic blood pressure (figs 14 and 15). This bacterial poison behaved, therefore, physiologically like histamine, but chemical examination of the total concentrated filtrate revealed the complete absence of this amine.

On the other hand, another pneumonia filtrate obtained from sputum 18 T produced a marked rise in blood pressure *in vivo* and a marked arterial constriction *in vitro*. Its behavior in this respect is therefore comparable to epinephrine, from which it differs, however, pharmacologically by causing intense bronchial constriction. Its reaction recalls tyramine, although chemical tests proved this substance to be entirely absent (figs 16 and 17).

The toxicity of these unknown poisons for guinea-pigs is marked. On intravenous injection 1 cc frequently kills a guinea-pig with respiratory failure, while the heart action is often unimpaired for a long time.

By means of continuous dialysis at reduced pressure for twenty-four hours,<sup>2</sup> it is possible to divide the active fractions into a nondialyzable that the active substance is diffusible through a semipermeable membrane residue and the diffusate. The pharmacologic activity resides completely in the latter, while the residue is physiologically without effect, showing and that it is, therefore, a crystalloid.

*Bacillus typhosus* Hopkins when grown in the histidine-glycerin-blood broth medium forms a poison which proved active when tested for bronchiolar and arterial contraction (fig 18). Histamine was completely absent. This fraction was dialyzed in our apparatus for twenty-four hours. Residue and diffusate were then tested after careful neutralization. Only the latter was physiologically active.

<sup>2</sup> Hanke, M. T., and Koessler, K. K. J. Biol. Chem. 66: 495-499, 1925.

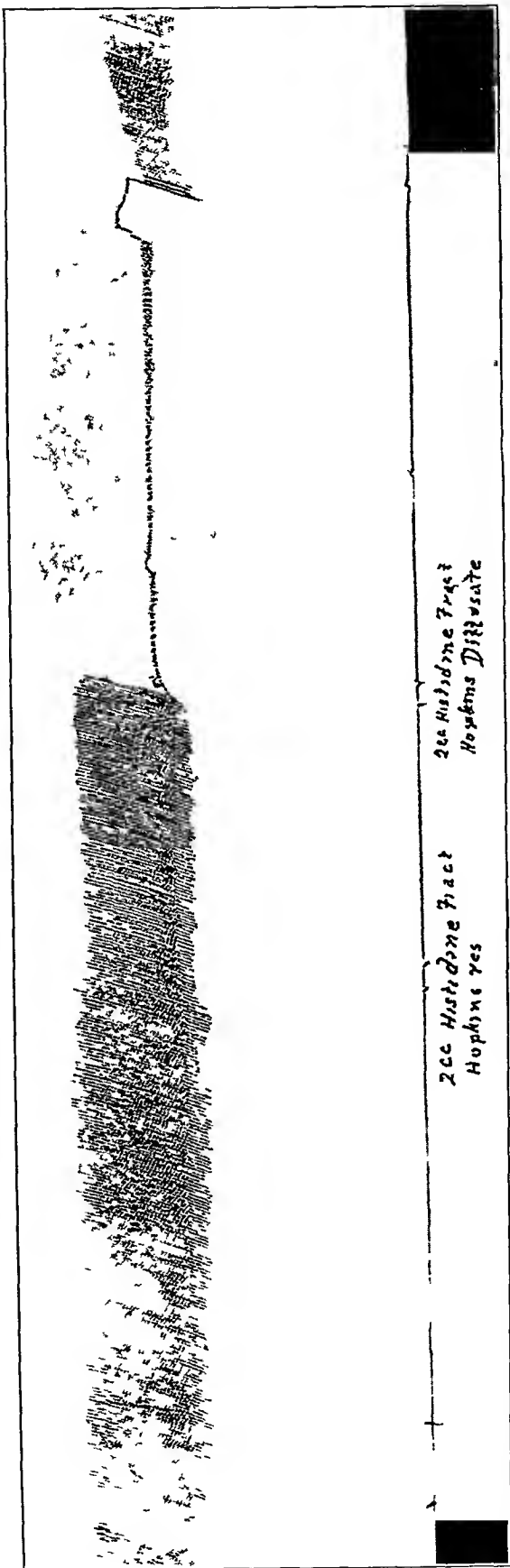


Fig 18

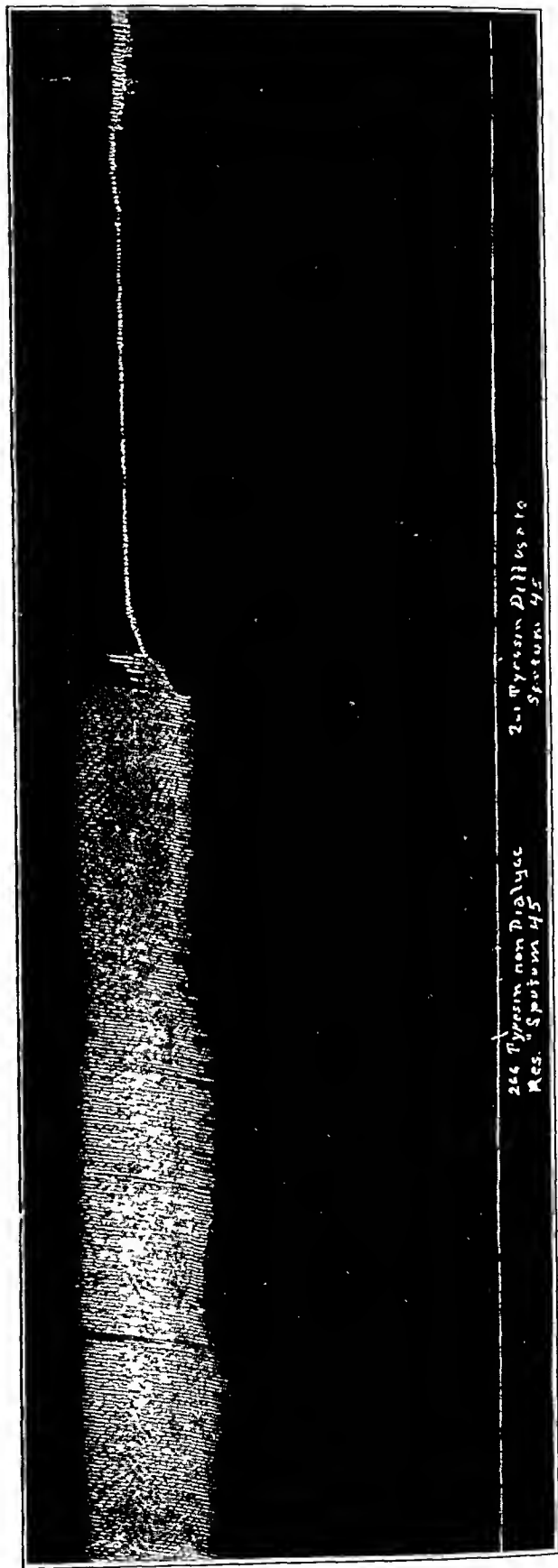


Fig 19

The same point is illustrated in figure 19, which was obtained from the culturing of sputum 45 (from a patient suffering from lobar pneumonia) in a tyrosine-blood broth medium. The amine fraction showed intense bronchospasm and arteriolar contraction. Tyramine was completely absent. After dialysis activity could be demonstrated only in the diffusate, the nondialyzable residue was without effect (fig 20).

Regarding the physical behavior and chemical nature of these poisons involved, no definite statements can be made at this time. They are not destroyed by heating to 100 F, and are not destroyed by treatment with 30 per cent sodium hydroxide solution or by strong acids. Since they pass into amyl alcohol in the presence of alkali they are probably noncarboxylated compounds of the nature of amines.

## COMMENT

It could be demonstrated that the mixture of micro-organisms contained in the bronchial secretion (sputum) and in other inflammatory

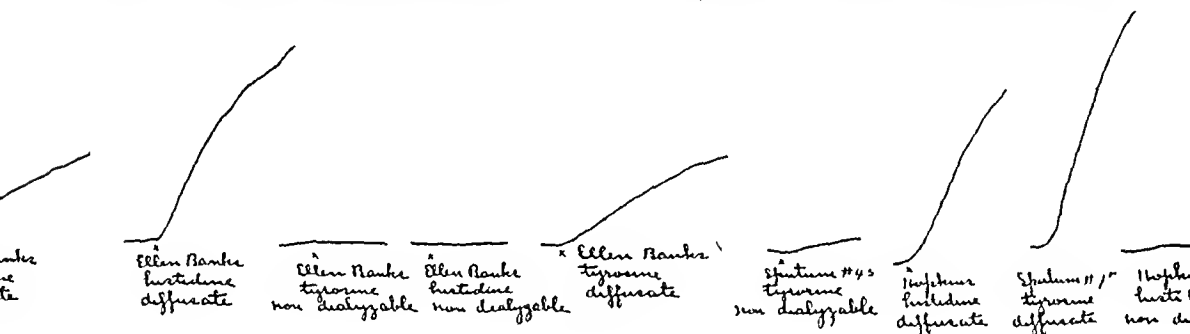


Fig 20

Figs 18, 19 and 20—Curves showing that the bronchoconstrictor and vasoconstrictor substances produced by bacteria are crystalloids, the nondialyzable residue is pharmacologically inactive.

exudates, e g, empyema fluid, leads in proper culture mediums to the formation of poisons of definite pharmacologic action. It is evident from our experiments (table 1, experiments 27, 30 and 33) that the formation of these poisons is not dependent on the addition of the amino-acids to our blood-broth-glycerin medium, since they are formed also without their addition. Certain isolated strains of pneumococci, streptococci, *B coli*, *B typhosus*, and many other common micro-organisms form such poisons, which have the faculty of contracting blood vessels in vitro and causing bronchospasm in the living guinea-pig. The application of these observations to human pathology might invite the objection that all these poisons formed are the result of autolytic processes of the micro-organisms. That a large number of the organisms are alive in our cultures after fourteen days we know. Autolytic processes undoubtedly proceed side by side with the life and growth of the micro-organisms. But whatever these soluble poisons are—pure cell

proteins, endotoxins or exotoxins, or products due to autolysis—similar conditions which exist in our *in vitro* experiments will hold true for their production *in vivo*. Most foci of infections in the human body, such as tonsils, infected sinuses, sacculated empyemas or the infected bronchial mucosa, may be looked on as tissue cultures *in vivo*, from which absorption of poisons takes place from time to time. The relation to bacterial poisons of certain forms of dyspnea due to bronchiolar constriction is of great interest to the clinician. The existence of the infectious type of bronchial asthma, or asthmatic bronchitis, whose clinical and immunologic analysis sets it apart from the forms of asthma in which the bronchospasm is produced by an allergic intoxication, finds experimental verification in our observations.

The relation of vascular spasms due to bacterial poisons to certain forms of arterial hypertension receives support by the experiments reported here. Thus, leading clinicians have thought for many years that patients who have had typhoid fever have a tendency to hypertension in later life. Almost all strains of micro-organisms of the typhoid group studied yielded a filtrate that caused intense arteriolar constriction *in vitro*. But it is the streptococcus, the most ubiquitous of all pathogenic organisms in man, which furnishes the largest number of strains that form vasoconstrictor substances.

#### SUMMARY

Filtrates from bacterial growth were studied for their pharmacologic action on arteries and bronchi.

The mixture of micro-organisms contained in bronchial secretions (sputum), empyema fluid, tonsils and other foci of infection, when grown in a blood-broth-glycerol-amino-acid medium, forms substances that cause arterial constriction *in vitro* and bronchial constriction in the living pithed guinea-pig.

Certain strains of many common pathogenic micro-organisms—pneumococci, streptococci, *B. coli*, *B. typhosus* and *B. paratyphosus*—form substances in a blood broth-glycerin-amino-acid medium which cause arterial constriction *in vitro* and bronchial constriction in the living guinea-pig.

The action of the poisons is frequently a selective one. A filtrate that causes bronchiolar constriction may have no action on the smooth musculature of the arteries and vice versa. A spasm of both bronchi and arteries is, however, frequently obtained with the same filtrate.

Some poisons causing arterial constriction *in vitro* cause a marked rise in blood pressure *in vivo*, thus exhibiting an epinephrine-like behavior. Others which cause constriction of the arteries *in vitro* lead to a fall of blood pressure *in vivo*, acting thus like histamine.

The active substances formed are only in a small percentage chemically identifiable as histamine and tryptamine. In the majority of cases we have to deal with poisons of unknown chemical constitution.

The chemical behavior of the active fraction of the bacterial filtrate suggests that these substances are probably amines.

The bacterial poisons studied may be involved in the production of certain forms of bronchiolar spasm in man (bacterial asthma) and others in the production of certain forms of arterial hypertension.

# SPECTROPHOTOMETRIC ANALYSIS OF BLOOD SERUM IN NORMAL AND PATHOLOGIC CONDITIONS

## STUDY I \*

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As a part of a large group of studies which have been in progress for a number of years at the Mayo Clinic, it has been necessary to learn whether the yellow pigment in the blood serum of patients suffering from pernicious anemia, hemolytic jaundice, obstructive jaundice and severe toxic diseases, such as malaria, was the same substance and whether this pigment was present in smaller amounts in normal blood serum. The answer to this question obviously has much to do with the understanding of the formation of bile and the destruction of erythrocytes.

We have shown that following total removal of the liver,<sup>1</sup> a yellow pigment rapidly accumulates which is found in the blood serum, fat and urine of the animal. Intensive investigation of this phenomenon has led to the conclusion that the substance is bilirubin and is exactly like that found in the serum of animals in which jaundice has been produced by ligation of the common duct.<sup>2</sup> It has been further shown that this pigment is formed chiefly in the bone marrow, spleen and regions rich in reticulo-endothelial cells,<sup>3</sup> and that its formation goes on regardless of the presence of the liver. As a result of this work one may draw the tentative conclusion that erythrocytes are being broken down in the body all the time, chiefly at the site of, or by, reticulo-endothelial cells, and that this hemoglobin is by some process made into bilirubin, which is in turn excreted by the liver as bile. If for any reason the exit of bile is interfered with, it accumulates in the body and produces a condi-

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\* From the Section on Clinical Pathology, Mayo Clinic, and the Section on Physics, the Mayo Foundation.

1 Mann, F C, and Magath, T B. A Further Study of the Effect of Total Removal of the Liver, *Am J Physiol* **59** 484, 1922, *Die Wirkungen der totalen Leberextirpation*, *Ergebn d Physiol* **23** 212-273, 1924. Mann, F C, Bollman, J L, and Magath, T B. Studies on the Physiology of the Liver. IX. The Formation of Bile Pigment After Total Removal of the Liver, *Am J Physiol* **69** 393-409 (July) 1924.

2 Mann, F C, Sheard, Charles, and Bollman, J L. Studies on the Physiology of the Liver. XI. The Extrahepatic Formation of Bilirubin, *Am J Physiol* **74** 49-60 (Sept) 1925.

3 Mann, F C, Sheard, Charles, Bollman, J L, and Baldes, E J. The Site of the Formation of Bilirubin, *Am J Physiol* **74** 497-510 (Nov) 1925.

tion of jaundice, being eventually excreted by the kidneys. Thus, one may conclude that if, for any reason, blood is broken down too rapidly to be excreted, jaundice may result, even though there is no dissolution of the continuity of the bile tracts. Indeed, this has been demonstrated by spectrophotometric determinations and the van den Bergh reaction.

In order to test some features of this hypothesis, we have examined a number of serums by spectrophotometric methods. Samples of blood were taken from patients under the most careful conditions to avoid hemolysis. The centrifuge tubes, as well as the syringes and needles, were rinsed out with a physiologic solution of sodium chloride. Blood from the median basilic vein was carefully drawn into the syringe and carefully expelled into the tube. Without agitation, it was allowed to clot and the serum to be expressed in the icebox. The clear serum, after centrifugalizing, was mixed with a mixture of four parts of alcohol and one part of acetone, one part of serum to ten or twenty parts of the alcohol-acetone mixture according to the depth of color of the serum. After standing two hours the mixture was centrifugalized and the clear supernatant fluid analyzed in the spectrophotometer. All cloudy fluids were discarded as well as those showing spectral bands of oxyhemoglobin.

#### SPECTROPHOTOMETRIC METHODS AND PROCEDURES

The spectrophotometer used in these investigations was one brought out about a year or so ago by Keuffel and Esser and referred to in the literature as a "color analyzer"<sup>4</sup>. Figure 1 is a reproduction of a photograph of the instrument. Figure 2 is a cross-section diagram showing the parts of the machine and their arrangement both as to the spectrometric and the photometric operations. The instrument consists essentially of a lamp house carrying two magnesium carbonate blocks (cut from the same cake), which are placed at the rear, these blocks serve as sources of light for transmission through the receptacles containing the liquids to be examined. The beams of light reflected by the blocks, after transmission through two suitable openings in the front of the lamp house, enter the two receptacles containing the solution and the solvent, respectively. These tubes are placed in the proper positions before the entrance slit of the spectrometer by an adjustment on a vertical supporting rod. The spectrophotometer proper does not differ in fundamental principles from the ordinary constant deviation type of instrument except for the addition of a biprism, which is placed in front of the telescopic lens system, and an observing (exit) slit in the eyepiece. Throughout the series of observations which are being reported in this paper the entrance and exit slits were kept at constant or fixed values, following the initial adjustment of the entrance slit to give 100 per cent transmission from the magnesium carbonate blocks throughout the whole of the spectrum. A balance in the intensities of the light transmitted by the standard cell and by the solution under examination was made by means of a sector photometer, the intensity of the light transmitted by the standard cell only being varied. In the majority of the experiments described here, both containing tubes were 10 cm in length. The standard cell was filled with a mixture of alcohol (four parts) and acetone (one part), the other tube carried the solution to be examined (ordinarily one part of serum to ten or twenty parts of alcohol-acetone solution, depending on the depth of the color).

<sup>4</sup> Keuffel, C. W. A Direct Reading Spectrophotometer, *J. Optical Soc. Amer. and Rev. Scientific Instruments* **11** 403-410, 1925.

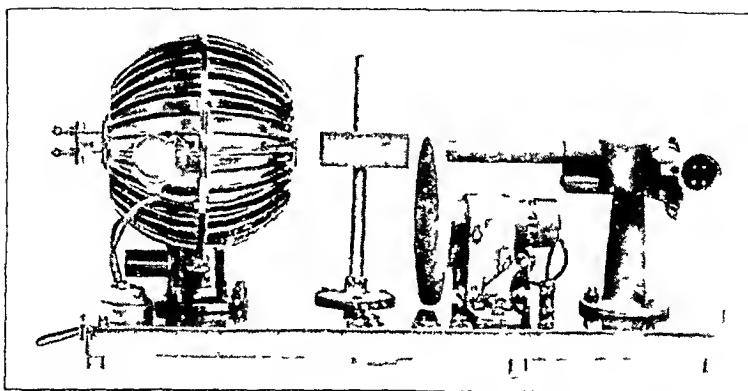


Fig 1—Spectrophotometer, or Keuffel and Esser color analyzer

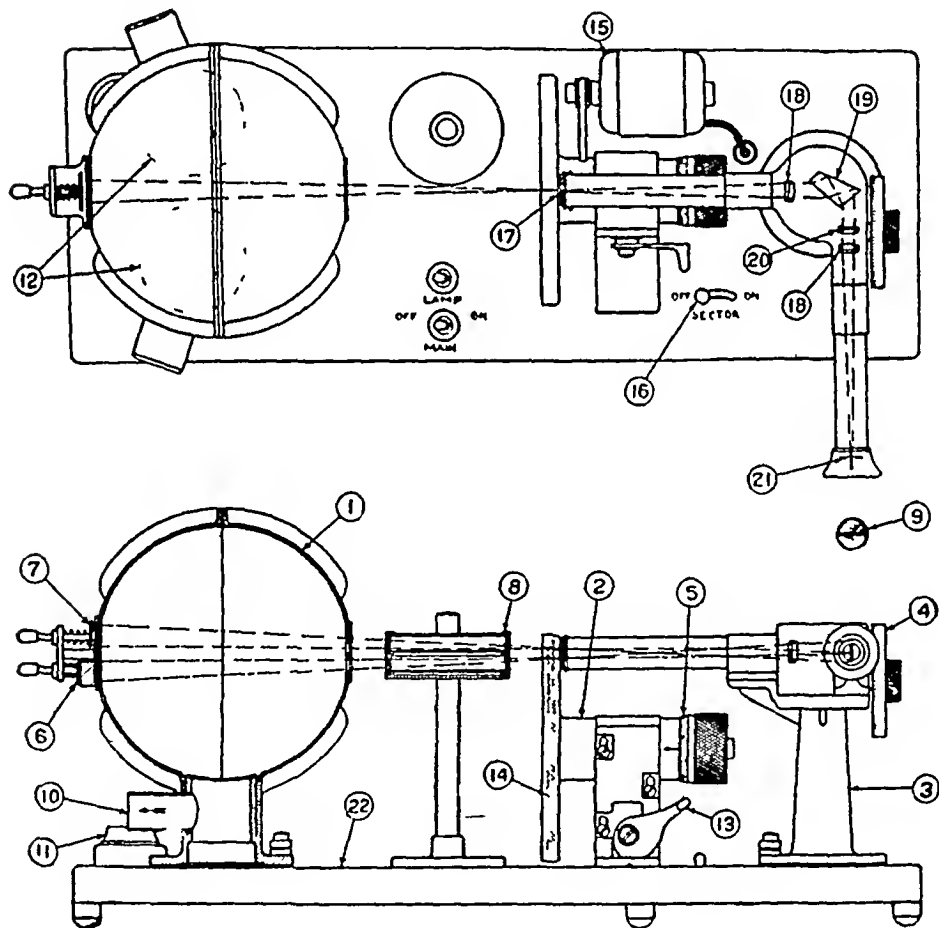


Fig 2—Cross-section diagrams of the spectrophotometer 1, lamp house, 2, photometer, 3, spectrometer, 4, wave length scale, 5, photometric scale, 6 and 7, magnesium carbonate blocks, 8, field of view through eye slit, 12, 400 watt lamps, 14, sector disks, 16, speed control rheostat, 17, entrance slit, 18, collimator objectives, 19, dispersion prism, 20, biprism, and 21, eye slit

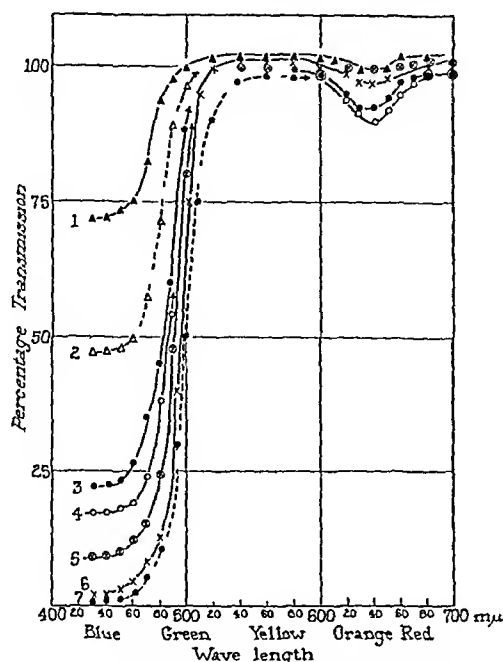


Fig 3—Spectrophotometric analyses of blood serums from selected cases, both normal and pathologic 1, normal, 2, normal with higher content of bilirubin, 3, malaria, 4, pernicious anemia, 5, hemolytic icterus, 6, obstructive jaundice, 7, bile from a normal person diluted to a degree sufficient to permit of spectrophotometric readings in the region 430 to 460 millimicrons. In the curves 1 to 6, inclusive, the dilution was kept constant at one part of clear serum to twenty parts of alcohol-acetone mixture.

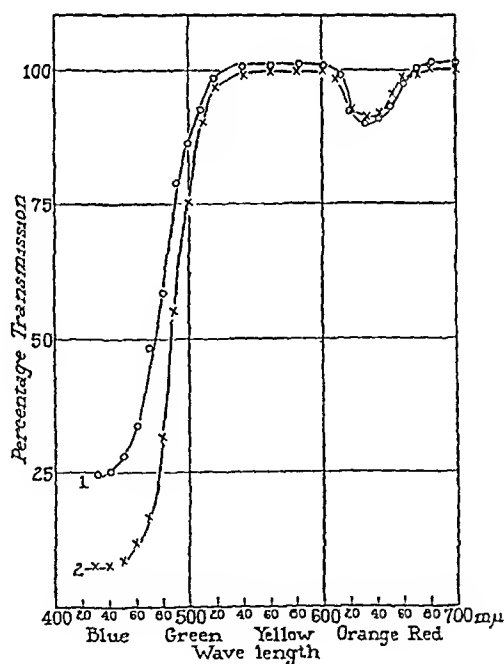


Fig 4—Spectrophotometric analysis in a selected case of pernicious anemia 1, before transfusion, and 2, after transfusion. The increased percentages of hematin (620 to 640 millimicrons) and of bilirubin (430 to 500 millimicrons) present in the condition shown in curve 2 as compared with that shown in curve 1 should be noted.

The method of getting the data shown in figures 3, 4 and 5 is as follows. White light is passed through the two containers placed in front of the housing which carries the rotating sectors, and is admitted to the spectrometer. The spectrometer is set at any desired wave length by means of a calibrated wheel. As an illustration, with a setting of 590 millimicrons (which is approximately the wave length of sodium yellow of the spectrum) the observer, on looking through the exit of the eye slit, sees two semicircular colored areas in juxtaposition, with the dividing line horizontal. Both halves of the circle will have the same hue (yellow), but not necessarily the same brightness or saturation value. The adjustment for the equality of brightness, or a match, is then made by varying the size of the sector opening in the rotating sectors placed in front of the spectrometer. The percentage transmission of the solution as compared to the percentage transmission of the liquid (alcohol) in the so-called standard cell is read directly from the calibrated drumhead. This drumhead is mechanically connected to the sectorized disks in such a manner as to permit rapid turning of it by hand, thus providing a quick way of varying the relative proportions of open sector and closed sector areas. In determining the percentage

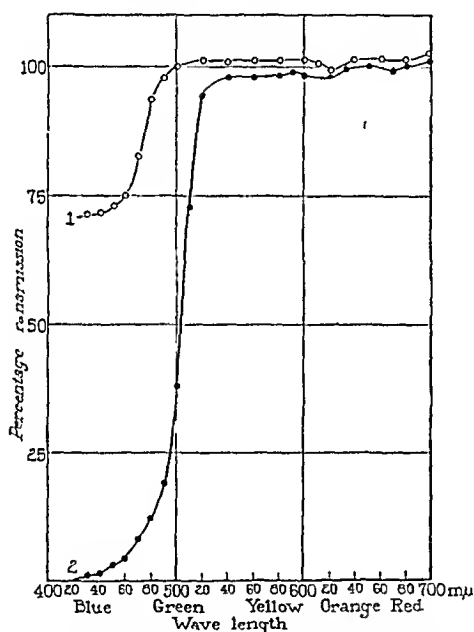


Fig 5—Spectrophotometric analyses of blood serums in dilution of one part of clear serum to twenty parts of alcohol-acetone mixture. Curve 1 is for a normal subject, curve 2 gives the results of the analysis in the case of a patient developing an intense jaundice following extensive hemorrhage in the gastrointestinal tract.

transmissions for any given wave length, it has been our custom to allow a few moments for the adjustment of the eye to the spectral hue under observation, and to record as the final reading for each wave length taken (ordinarily by steps of 10 millimicrons) the average of five determinations which do not vary more than from two to three points, respectively. After the measurement for equality of brightness for any given wave length has been made, the procedure, as outlined, is repeated for as many determinations and for as many spectral regions or wave lengths as are deemed necessary. A recent article on spectrophotometric studies on bilirubin<sup>5</sup> gives further details of these methods and the criteria which must be observed if an accurate comparison of data is to be possible.

5 Sheard, Charles, Baldes, E. J., Mann, F. C., and Bollman, J. L. Spectrophotometric Determinations of Bilirubin, *Am J Physiol* **76** 577-585 (May) 1926.

All of the data graphically shown in the curves of figure 3 are drawn on the basis of a uniform dilution of one part of serum to twenty parts of alcohol-acetone mixture in samples of blood from patients covering the range from normal to obstructive jaundice. In the actual experimental work, however dilutions of from 1:40 to 1:60 were often used for the reason that, in certain instances, such as in cases of obstructive jaundice, a dilution of 1:20 was not sufficiently low to permit of reading the transmissions in the wave length region of 430 to 470 millimicrons. It is, however, possible to compute the spectrophotometric transmissions for any specified wave length and for any degree of dilution of solution if one establishes some unit or standard of measurement. For this purpose Bunsen and Roscoe introduced the extinction coefficient,

symbolized by  $\epsilon$ . From Lambert's law  $\epsilon = -\frac{\log I}{X}$  in which  $I$  represents the

intensity of the transmitted light and  $X$  the depth of solution. As a standard, therefore, for our spectrophotometric measurements we have taken the value of the transmission  $I$  for a constant depth of solution  $X$  of 10 cm and for a given wave length of 440 millimicrons, and for a dilution of 1:20. Wave lengths from 430 to 470 millimicrons can be used, however, the one adopted

must be adhered to throughout the investigation. From Beer's law  $\frac{\epsilon_1}{\epsilon_2} = \frac{C_1}{C_2}$ ,

hence, the absorption of light by different concentrations of the same substance in the solvent is directly proportional to the concentration  $C$ . Therefore, from the laws of Lambert and Beer we are able to say that

$$\frac{\epsilon_1}{\epsilon_2} = \frac{C_1}{C_2} = \frac{-\log I_1}{-\log I_2}$$

It is possible by use of the foregoing formulas to calculate the transmission  $I$  for any wave length if  $C_1$ ,  $C_2$  and  $I_1$  are known. In this manner spectrophotometric data can be reduced to a constant dilution factor of 1:20, as in the curves of figure 3. In practice one can readily determine the spectrophotometric transmission for 440 millimicrons (or other wave lengths), for a specified strength of solution (for example, 1:5 and a depth of 10 cm) of blood serum from a person chosen as normal. By further dilution to, for example, 1:10, 1:20 and 1:40, and by taking the spectrophotometric readings for the wave length chosen, it is possible to plot on semilogarithmic paper a straight line showing the relationship between the logarithm of the percentage transmission of light ( $\log I$ ) for any specified wave length and the concentration  $C$  of the solution.

In general it was found that the amounts of pigment in the serum as shown by this method follow quite closely the amounts demonstrated by the van den Bergh method, except that the latter method does not give differences with accuracy when the amount is small.

## RESULTS

As can be seen, the type of the curve in all our cases (figs 3, 4 and 5), essentially normal persons, from the standpoint of jaundice, and those suffering from pernicious anemia, hemolytic jaundice, obstructive jaundice and malaria, is the same, these curves are exactly like those given by bile and therefore correspond to the spectral analysis of bilirubin. The difference is one of amounts only. If arbitrary units are devised to show the comparative amounts of bilirubin in the serum, one finds that, in the order of amount, the cases are distributed thus: in cases of normal persons, the least amount, in cases of slight anemia and nervous exhaustion, next in amount, then malaria, pernicious

anemia, hemolytic icterus and, finally, obstructive jaundice or intense jaundice without obstruction of the biliary passages. A careful necropsy

The last condition was noted in a patient, and was of particular interest because he presented the apparent paradox of an increasing jaundice without obstruction of the biliary passages. A careful necropsy was performed and particular attention was paid to the liver and its passages, with the result that no specific abnormalities were found. The hemorrhage due to ulcers was of several weeks' duration and bleeding from a large ulcer had been almost continuous, the gastro-intestinal tract being almost completely filled with old blood, and the walls of the intestine markedly discolored. Unfortunately, the record as to whether the reaction to the van den Bergh test was direct or indirect is lacking. Since that time, however, we have seen another case almost exactly like

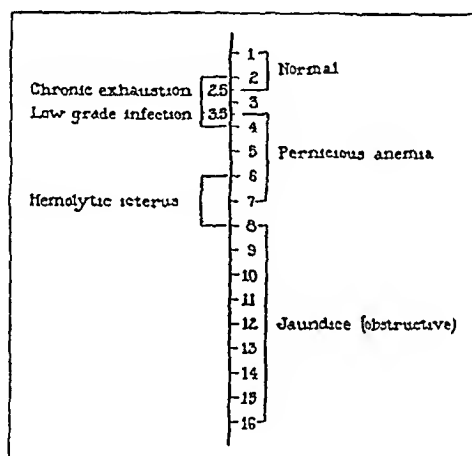


Fig 6—Amounts (expressed in arbitrary units) of bilirubin as determined spectrophotometrically in normal and various pathologic conditions

this one, in which death resulted from gastro-intestinal hemorrhage, the content of bilirubin by the van den Bergh test was even higher, and the reaction was direct. While it is possible that jaundice was due to other factors, necropsy and the clinical study of the cases suggests that jaundice may be due to the absorption of blood through the gastro-intestinal tract. However, numerous experiments have been made which show that hemoglobin is not absorbed through the gastro-intestinal tract, and that the bilirubin content of the blood is not increased by ingestion of whole blood. As is evident in our series of cases, high bilirubin serum content is quite closely correlated with anemia and hemorrhage, and these may be the essential factors in this case rather than absorption of blood through the intestinal wall.

If the low normal content of bilirubin is designated as one unit, then deep jaundice may be represented as from thirteen to seventeen units. Figure 6 illustrates the distribution. It is important to note that there

are no sharp dividing lines and that the values overlap each other. Definite changes in the color of the skin, from a light lemon tint to a deep dark greenish yellow, are seen in all cases having a value of 3.5 units or more.

Almost all curves of serum show a slight absorption, between 610 and 630 millimicrons, which for the present has been interpreted as being due to hematin. Normally this band is faint, in malaria (active

*Spectrophotometric Values of Blood Serum*

Case	Hemo- globin, Eryth- rocytes, (Dare Method)	per Cent Mill- ions	Van den Bergh Test, Mg	Spectro- photo- metric Values†	Spectro- photo- metric Value After Trans- fusion	Van den Bergh Test After Trans- fusion, Mg	Hematin	Diagnosis
1	78	4.36		1.0			1—	Migraine
2	40	2.45		1.0			Trace	Myocardial disease, tumor of stomach (?)
3	78	4.50		2.0			Trace	Myocardial disease, constipation
4	75	4.97		2.1			Trace	Congenital club-feet, septic tonsillitis
5	76	4.18		2.5			2	Chronic nervous exhaustion, septic tonsillitis
6	75			2.6			1+	Chronic nervous exhaustion
7	65	4.45		2.75			Trace	Chronic tonsillitis, indefinite right-sided pain
8	80	4.58		3.0			1	Chronic nervous exhaustion
9	76			3.0			2	Cholecystitis with cholelithiasis, no jaundice
10	77			3.25			Slight	Colloid goiter
11	42	3.44		3.5			Slight	Endocarditis, glomerulonephritis
12	30	2.40	1.83*	3.75	4.6	1.36*	3	Pernicious anemia
13	75	4.39	1.5*	4.0			Slight	Salpingitis
14	52	3.22	2.0*	4.1			3	Cerebrospinal syphilis, acute malaria
15	30	2.50		4.2			1	Carcinoma of the cecum
16			2.3*	4.4			3	Cerebrospinal syphilis, acute malaria
17	25	1.36		4.4	4.4	1.5*	3	Pernicious anemia
18	30	2.05	1.81*	4.46	3.56	1.36*	3	Pernicious anemia
19	30	1.93		4.5			3	Pernicious anemia
20	30	1.78		4.5	7.6		3	Pernicious anemia
21	23	0.98	2.65*	4.75	5.9	2.34	3	Pernicious anemia
22	55	3.13	4.2*	7.0			1	Hemolytic icterus
23	33	2.00		7.5			3	Pernicious anemia
24	31	2.86	10.4	10.2			1	Obstructive jaundice
25	65	4.19	14.9	10.72			2—	Malignant disease of liver with obstructive jaundice
26	54	3.33	15.7	12.5			1	Obstructive jaundice
27	39	2.74	11.5	16.2			Slight	Operation for hyperprostatism, severe gastro-intestinal hemorrhage with marked jaundice, septicemia, no biliary obstruction

\* Indirect reaction

† In terms of arbitrary unit

cases) and pernicious anemia, it is deepest, while in hemolytic and obstructive jaundice it is intermediate. The presence of hematin in serum has been discussed before,<sup>6</sup> and it was pointed out that the more hematin present in blood serum, the more destruction of erythrocytes has taken place.

6 Mann, F. C., Sheard, Charles, Bollman, J. L., and Baldes, E. J. The Formation of Bile Pigment from Hemoglobin, *Am. J. Physiol.* **76**: 306-315 (April) 1926.

As can be seen from the accompanying table, there is usually an increase in the bilirubin content of the blood following transfusion in cases of pernicious anemia, which points to the possibility that either some of the red cells are broken down in the patient's body or are injected already hemolyzed as a result of the process of bleeding, mixing with citrate and injection. Since the results of the van den Bergh test are within normal limits in these cases, no help can be expected from the test. It seems worth while studying this further, since some correlation might be established between the amount of hemolysis after transfusion and the degree of reaction on the part of the patient.

There have been many studies comparing the bilirubin of obstructive with that of hemolytic jaundice. One of the most thorough is that of van den Bergh,<sup>7</sup> who came to the conclusion that they were essentially different, basing his conclusions on the Ehrlich diazo reaction. The reaction is direct in obstructive jaundice and indirect in hemolytic jaundice. Also the bilirubin was more readily oxidized in the former case and was more readily adsorbed than the other form to the protein precipitated by the alcohol in performing the indirect test. Grunenberg<sup>8</sup> found a difference in solubility in chloroform between the two types. Hoover and Blankenhorn<sup>9</sup> found that, while "obstructive" bilirubin dialyzed easily, the "hemolytic" bilirubin would not dialyze until alcohol was added. This work was confirmed by Leschke<sup>10</sup> and Brule, Garban and Weissmann.<sup>11</sup> The nature of the two types of bilirubin has been hypothesized by many. Blankenhorn<sup>12</sup> and van den Bergh both thought that the hemolytic form was linked with a protein or other substance in the serum, Feigl and Querner<sup>13</sup> suggested a lipid linkage, and perhaps the linkage is with cholesterol as suggested by Rosenthal and Holzer,<sup>14</sup> and by Adler.<sup>15</sup> Adler and Strauss<sup>16</sup> considered the colloid

7 Van den Bergh, A. A. H. *Der Gallenfarbstoff im Blute*, Leiden, S. C. Van Doesburgh, 1918.

8 Grunenberg. *Aussprache, Verhandl. d. Kong. f. inn. Med.* **34** 112-114, 1922.

9 Hoover, C. F., and Blankenhorn, M. A. *Dissociated Jaundice*, *Arch. Int. Med.* **18** 289-303 (Sept.) 1916, also *Tr. Am. Phys.* **31** 243-260, 1916.

10 Leschke, E. *Aussprache über Ikterus*, *Berl. klin. Wchnschr.* **58** 848, 1921.

11 Brule, M., Garban, H., and Weissmann, C. *L'étude de la bilirubine du serum sanguin, peut-elle aider à reconnaître la nature d'un ictère*, *Presse med.* **30** 986-988, 1922.

12 Blankenhorn, M. A. *Acholic Jaundice*, *Arch. Int. Med.* **27** 131-134 (Jan.) 1921.

13 Feigl, J., and Querner, E. *Bilirubinämie in ihren psychologisch-chemischen Beziehungen mit besonderer Berücksichtigung der diagnostischen Bedeutung*, *Ztschr. f. d. ges. exper. Med.* **9** 153-250, 1919.

14 Rosenthal, F., and Holzer, P. *Beiträge zur Lehre von den mechanischen und dynamischen Ikterusformen. I. Mitteilung*, *Deutsches Arch. f. klin. Med.* **135** 257-280 (March) 1921.

15 Adler, A. *Chemisch-physikalische Untersuchungen an Gallenfarbstoffen und Cholesterin*, *Verhandl. d. Kong. f. inn. Med.* **34** 72-73, 1922.

16 Adler, Erich, and Strauss, Leo. *Beitrag zum Mechanismus der Bilirubinreaktion im Blut. II. Mitteilung*, *Klin. Wchnschr.* **1** 2285-2286, 1922.

nature of the two serums as a factor Andrewes<sup>17</sup> concluded that the two forms were different, basing his conclusion on the van den Bergh reaction, the chloroform solubility test, adsorbability to precipitated proteins, oxidation in iodine, Fouchet's<sup>18</sup> test, dialysis and permeability of the kidneys to it. He thought the difference was not due to linkage to other substances, and that both types were probably present in fresh bile. Either standing or heating caused the obstructive type to go over to the hemolytic type. He offered evidence to support the view that the hemolytic type was identical with hematoidin and that the real difference between obstructive and hemolytic bilirubin lay in a difference in physical state, the latter possibly being in a fine suspension instead of a solution.

Blankenhorn<sup>19</sup> came to the conclusion that bile pigment is frequently found in the blood in cases of pernicious anemia and accounts for the jaundice. He used the tests of Gmelin, Pettenkofer and the spectroscope.

Our experiments show that the spectral analysis of serum obtained from essentially normal persons and of that from persons with jaundice from various causes are alike. Since the serums were treated with an alcohol and acetone mixture before the spectral analyses were made, it might be argued that if there were differences in the bilirubins we had destroyed them in the process of preparation. In other words, it might be contended that we changed all the "direct" bilirubin to "indirect" bilirubin. We tested this by examining specimens in the spectrophotometer before the addition of alcohol, and found the results to be the same as when examined after the addition of alcohol. The blood was allowed to clot and the clear serum was diluted with sodium chloride solution. Of particular interest was the case of hemolytic icterus, which, with an indirect van den Bergh reaction of 4.2 mg. for each 100 cc., gave the same spectrophotometric curve before the addition of alcohol-acetone as after. If the bilirubin contained in blood serums differs, it cannot be shown spectrophotometrically. While it is evident from the van den Bergh reaction that there are some differences in bilirubins, possibly in their physical state or in the nature of a loosely combined state, fundamentally the substance is one and the same whether from so-called obstructive or hemolytic causes, and the common source is evidently the erythrocytes.<sup>20</sup> Furthermore, to argue that the substance

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17 Andrewes, C. H. The Nature of the Difference Between the Bilirubins of Obstructive and Hemolytic Jaundice, *Brit J Exper Path* **5** 213-219 (Aug) 1924.

18 Fouchet, A. Methode nouvelle de recherche et de dosage des pigments biliaires dans le serum sanguin, *Compt rend Soc de biol* **80** 826-828, 1917.

19 Blankenhorn, M. A. The Bile Content of the Blood in Pernicious Anemia, *Arch Int Med* **19** 344-353 (March) 1917.

20 Mann and Magath (footnote 1). Mann, Sheard, Bollman and Baldes (footnote 6).

in hemolytic icterus is hematoidin is beside the point since Rich and Baustead<sup>21</sup> have shown that hematoidin and bilirubin are identical

Naturally, it would be important to understand the method by which bilirubin, which must be interpreted as a result of destruction of erythrocytes, is retained in the blood, and certain explanations seem at hand

A small amount of bilirubin must always be present in the body and represent the daily break-down of erythrocytes in the tissues. This is excreted as bile at a certain rate, which probably varies with the emptying of the gallbladder and the normal activity of the liver. There are probably two methods and a combination of these two that result in retention of bilirubin: the first, too rapid destruction of erythrocytes, and the second, too slow hepatic excretion. Obviously, retention of bilirubin in obstructive jaundice is explained by the mechanical obstruction at the biliary outlet and the damming back of the pigment. Conceivably this may result in increased destruction of erythrocytes, due to the hemolytic action of bilirubin and bile salts, and, indeed, secondary anemia in cases of obstructive jaundice is the rule. Furthermore, it is interesting to note that in obstructive jaundice erythrocytes show an increased resistance, which points to the fact that the more fragile cells have been broken down. This condition also obtains in pernicious anemia.

In hemolytic icterus we deal with an inherited fragile erythrocyte, which probably explains the jaundice, since it is obviously broken down more readily. In many cases there is intermittent obstruction due to small stones. Here, again, the breakdown of erythrocytes results in jaundice which, in turn, increases the breakdown and the vicious circle is established. In malaria rapid mechanical rupture of the erythrocytes, together with probable impairment of the function of the liver, results in the temporary increase of serum bilirubin.

The explanation of the mechanism in pernicious anemia is not at hand, but we offer as a possibility that, due to some cause, perhaps infection, rapid erythrocytic destruction is started in the body, that this resulting increase in the bilirubin content of the blood creates further destruction, and that the vicious circle is thus established. The retention is physiologic as a result of hepatic injury, due to infection and the unusual load it has to carry, and the flood of bilirubin is unable to get out. On this theory one would expect any method of draining the liver or causing a greater output of bile to be beneficial, as has been noted from time to time in the treatment.

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21 Rich, A. R., and Bumstead, J. H. On the Identity of Hematoidin and Bilirubin, *Bull. Johns Hopkins Hosp.* 36: 225-232 (April) 1925.

## CONCLUSIONS

We have shown that yellow pigment in the blood serum is bilirubin in normal persons, and in those suffering from malaria, pernicious anemia, hemolytic icterus and jaundice due to obstruction of bile. The degree of bilirubinemia varies so that the order named indicates the relative amounts. If the bilirubins are different, it is not shown in the type of spectrophotometric curve.

Usually one hour after transfusion in cases of pernicious anemia, the serum shows an increase in bilirubin.

Any process resulting in too rapid destruction of blood or too slow excretion of bile results in retention of bilirubin. Combinations of both factors probably play a part in the clinical picture and the spectral analysis. Fundamentally all jaundice is hemolytic.

# FUNCTIONAL DIASTOLIC MURMURS AND CARDIAC ENLARGEMENT IN SEVERE ANEMIAS\*

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The occurrence in patients with pernicious anemia of fatty infiltration of the heart manifested at the necropsy table by the so-called "tigering" of the heart muscle is well known. Dilatation of the heart as well as the presence of so-called "hemic" systolic murmurs are also matters of common observation. These changes are of little clinical interest or importance, so that ordinarily but slight attention is paid to the heart in patients with this disease. The following two cases of pernicious anemia, which presented classical physical signs of chronic valvular heart disease, but in which at necropsy the valves were normal in every respect, illustrate a cardiovascular symptomatology in pernicious anemia which deserves more attention, for it is not unusual.

CASE 1—G S, a woman, aged 29, entered Montefiore Hospital, Oct 5, 1925, with the diagnosis of pernicious anemia. She had been sick for about one year, complaining chiefly of weakness. During this year she had received eight transfusions of blood. On admission she appeared well nourished, slightly dyspneic at rest, with a brownish yellow skin. The hemoglobin was 16 per cent and the red cells numbered 560,000, the white cells 2,400 per cubic millimeter. The differential count showed 82 per cent polymorphonuclears, 16 per cent lymphocytes, and 1 per cent each of eosinophils and basophils. There was macrocytosis, poikilocytosis and anisocytosis. The test meal revealed an achylia gastrica. The heart, both by percussion and by roentgen ray, was slightly enlarged. Noteworthy was the area of dulness in the second interspace just to the left of the sternum, which on the roentgenogram (fig 1) showed as a prominence of the conus arteriosus. A short presystolic thrill was felt at the apex. The heart sounds at the apex were forcible. The first sound was preceded by a short rumbling presystolic murmur and accompanied by a systolic murmur. The second pulmonic sound was accentuated. In the fourth interspace 1 inch to the left of the sternum a gushing diastolic murmur was audible. There was a systolic murmur at the base. The pulse was full and collapsing, its rate was about 88. The blood pressure was 86 systolic and 42 diastolic. The electrocardiogram showed slight right ventricular predominance. The patient died of bronchopneumonia one week after admission. The necropsy performed by Dr David Seecof revealed excess iron deposits in the liver and kidneys and fatty infiltration of the heart. The heart weighed 260 Gm, was of average size and had a moderate amount of subpericardial fat. The right side was moderately dilated and strikingly flabby. The tricuspid valve admitted four fingers. There was some dilatation of the pulmonary conus. All the valves were normal. The left ventricle showed no abnormalities aside from "tigering" of the myocardium seen through the thin endocardium. The measurements of the valve orifices were as follows: pulmonary 7.5 cm, aortic, 7 cm, mitral, 8 cm, and tricuspid, 13 cm. The right ventricular wall measured 4 mm, the left, 10 mm. The coronary arteries were slightly dilated and contained a few scattered yellowish atheromatous plaques.

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CASE 2—C A, a woman, aged 33, was admitted to Montefiore Hospital, Aug 9, 1925, with a diagnosis of pernicious anemia, which had first been made five years before. A splenectomy had been performed two and a half years before her admission to the hospital. She had had eight transfusions of blood. On admission she appeared pale but well nourished, with a brownish pigmentation of the skin. She was orthopneic and had considerable ascites and a massive edema of the legs. The hemoglobin was 12 per cent. The red cells numbered 680,000, the white cells 5,600 per cubic millimeter. There were 48 per cent polymorphonuclears and 46 per cent lymphocytes. There were many nucleated red blood cells. Anisocytosis and macrocytosis were present. Gastric analysis revealed an acidity. The heart was enlarged both to the right and to the left. No thrills were palpable. The first sound at the apex was impure and rumbling and followed by a rough systolic murmur which was transmitted to the axilla. A high pitched inconstant

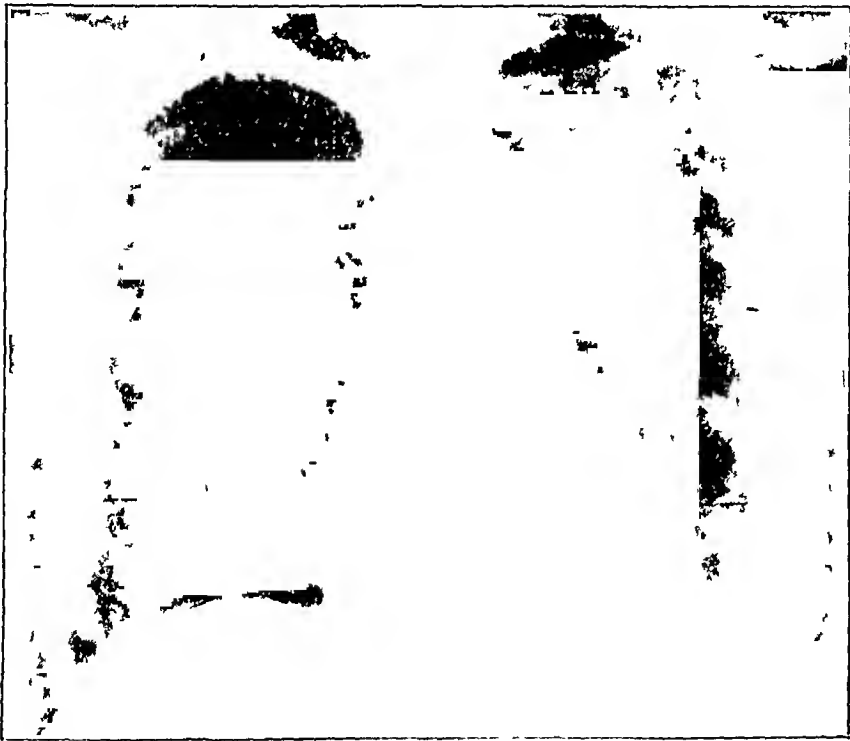


Fig 1 (case 1)—Heart showing enlargement and prominence of conus pulmonalis

soft diastolic murmur was audible at the fourth left intercostal space. The cardiac rhythm was regular, the rate 86. The blood pressure was 104 systolic and 44 diastolic. The pulses were full and readily compressible. The teleroentgenogram (fig 2) showed a greatly enlarged heart with the following dimensions: median left, 13.4 cm, median right, 6.7 cm. The electrocardiogram showed left ventricular predominance. The patient continued in the hospital for three and one half months with little change in her condition and finally died from pyelonephritis. Anatomic examination revealed a heart weighing 450 Gm. The epicardial fat was increased in amount. Hypertrophy and dilatation of the left ventricle were marked, of the right ventricle slight. There were no abnormalities of the valves, but the valvular orifices were dilated. The heart muscle was pale but showed no "tigering." Microscopic examination showed slight fatty infiltration of the muscle fibers.

The first of these cases exhibited practically all the classical signs of mitral stenosis, as well as an aortic diastolic murmur, and the second

presented apparently unmistakable signs of aortic insufficiency, yet in both instances all the heart valves were found anatomically intact at necropsy. Although it is common knowledge that systolic murmurs are often of functional origin, diastolic murmurs are usually regarded as rather convincing evidence of organic valvular disease. Isolated cases of diastolic murmurs in the absence of valvular lesions have been described in patients with marked hypertension<sup>1</sup> with dilatation of the aorta, with adherent pleura and pericardium,<sup>1</sup> and with diseases such as actinomycosis of the thorax, which distorts the relationship of the heart and the aorta.<sup>2</sup> The Graham-Steell murmur of relative pulmonic insufficiency belongs in the same category. This murmur is found particularly in patients with severe mitral stenosis,<sup>3</sup> but has been described in various other conditions that raise the pulmonary blood pressure,<sup>4</sup> as well as accompanying an artificial pneumothorax which resulted in a drag on the pulmonary conus.<sup>5</sup>

It appears, however, that functional diastolic murmurs have been noted most often in patients with severe anemias. Friedreich<sup>6</sup> was probably the first to describe a patient with secondary anemia in whom a diastolic murmur was heard during life, and in whom the necropsy revealed normal valves. Subsequently von Noorden<sup>7</sup> described three similar cases, one of which came to necropsy. In one the murmur was diastolic, and in two it was presystolic. In one patient the murmur disappeared as the anemia improved. Sahl<sup>8</sup> observed two patients with severe secondary anemia in whom he found cardiac enlargement as well as a diastolic murmur at the left border of the sternum. He believed that the altered condition of the blood caused the murmur. More recently Cabot<sup>1</sup> and Ortner<sup>2</sup> have reported similar observations in a few patients with pernicious anemia and have suggested that the murmur is determined by a relaxation of the aortic ring. Morse<sup>9</sup> noted

1 Cabot, R. C., and Locke, E. A. *Bull. Johns Hopkins Hosp.* **14** 115, 1903.  
Barie, E. *La Vraie et les Pseudo-Insuffisances Aortiques*, *Arch. gen. de med.* **1** 257, 1896.

2 Ortner, N. *Ueber akzidentelle diastolische Aortengeräusche*, *Med. Klin.* **19** 408 (March 31) 1923.

3 Steell, G. *M. Chronicle*, Manchester, **8** 99, 1888. *Internat. Clin.* **3** 144, 1898.

4 Litten. *Charité Annalen* **3** 182, 1878. Becker, E. *Beitrag zur Kenntnis der accidentellen diastolischen Herzgeräusche*, *Deutsches Arch. f. klin. Med.* **121** 207, 1917.

5 Lublin, A. *Zur Aetiologie akzidenteller diastolischer Herzgeräusche*, *Deutsch. med. Wchnschr.* **47** 1254 (Oct. 20) 1921.

6 Friedreich, N. *Virchows Handbuch der specifischen Pathologie und Therapie* **2** 227, 1861.

7 Von Noorden, C. *Untersuchungen über schwere Anämien*, *Charité Annalen* **16** 217, 1891.

8 Sahl, H. *Ueber diastolische accidentelle Herzgeräusche*, *Cor. Bl. f. Schweiz. Aerzte* **25** 33, 1895.

9 Morse, J. L. *Arch. Pediat.* **41** 559 (Aug.) 1924.

diastolic murmurs with water hammer pulse and pistol shot sounds in the arteries in infants and children with marked anemia, and observed their disappearance as the condition of the child improved. Finally, Kraus<sup>10</sup> heard diastolic murmurs in eight of forty-seven patients with pernicious anemia which he personally observed, and found them reported in ten of eighty-three cases that he collected from the literature.

We have reviewed the case histories of thirty-nine patients with pernicious anemia who have been treated at Montefiore Hospital. Diastolic murmurs were noted in six cases of this series. The murmur usually was heard best at the fourth intercostal space to the left of the sternum, but sometimes was apical. It was inconstant, but its disappearance was not always paralleled by a change in the blood picture or in the condition of the patient. One other patient presented an apical rumbling presystolic murmur, and two of the patients with aortic diastolic murmurs had apical presystolic murmurs as well.

Enlargement of the heart in anemic patients has often been noted. In the earlier literature there are many references to increased heart size in chlorosis. For instance, Gautier<sup>11</sup> found cardiac enlargement clinically in twenty of twenty-two patients with severe chlorosis. He noted, too, that with the increase in red blood cells and hemoglobin the heart rapidly receded in size. Subsequent studies revealed cardiac enlargement in many patients with pernicious anemia. Kraus<sup>10</sup> found cardiac dilatation in thirty of his forty-seven cases of pernicious anemia. The heart was enlarged to percussion. Large hearts, unexplained by valvular lesions or hypertension, were found by Wallgren<sup>12</sup> in six of seven, and by Cabot<sup>13</sup> in twenty-two of twenty-three patients with pernicious anemia who came to necropsy, and Strieck<sup>14</sup> reported that 30 per cent of a series of 165 patients with pernicious anemia had enlarged hearts. Of the thirty-nine patients observed at Montefiore Hospital, twenty-three had enlargement of the heart to the left, occasionally to the right, as determined by percussion. In six instances in which teleoroentgenograms were taken, this increase in heart size was verified objectively. All the twelve cases that came to necropsy showed cardiac dilatation. The average heart weight was 330 Gm, the smallest

10 Kraus, F. Die klinische Bedeutung der fettigen Degeneration des Herzmuskels schwer anämischer Individuen, *Berl klin Wchnschr* **42** V, 1905.

11 Gautier, E. Ueber die morphologischen Veränderungen des Herzens bei der Chlorose auf Grund klinischer Beobachtungen, *Deutsches Arch f Klin Med* **62** 120, 1899.

12 Wallgren, A. Die Arterien der Niere und der Blutdruck, *Acta med Scandinav* **56** 356, 1922.

13 Cabot, R. C. Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 19.

14 Strieck, F. Zur Symptomatologie der Biermerschen Krankheit, *Med. Klin* **20** 1538 (Nov 2) 1924.

250, the greatest 460 Gm. Only three hearts weighed less than 300 Gm. Yet there was little apparent hypertrophy of the ventricular walls. The dilatation involved all the chambers of the heart, including the pulmonary conus in four cases. "Tigering" of the myocardium was present in only one-half the cases. In all instances the valves were normal, except for small atheromatous flecks on the aortic leaflet of the mitral valve in a few cases.

The mitral configuration of the heart with bulging or prominence of the so-called left auricular salient in the roentgenogram, which was



Fig 2 (case 2) —Heart showing great enlargement and mitral configuration

noted by Kraus in 10 per cent of his patients with pernicious anemia, is well shown in our illustrations.

That heart changes similar to those that have been described may accompany severe secondary anemia as well is evidenced by the following two cases.

CASE 3—A. N., a man, aged 53, was admitted to Montefiore Hospital, Nov. 18, 1918, complaining of epistaxis, dyspnea, precordial oppression, vertigo and polyuria. These symptoms dated from an attack of pneumonia one year previously, although he had had frequent copious nosebleeds for about ten years. The patient was pale and thin. Scattered over the skin, the tongue and the nasal mucosa were many small telangiectases from 1 to 6 mm. in diameter. The lungs showed emphysema and bronchitis. The heart was not much enlarged to percussion but roentgen-ray

examination revealed enlargement to the left but no aortic widening. Systolic murmurs were heard at the apex and at the base. The liver was large and nodular. The pulse rate was between 80 and 90, the blood pressure was 118 systolic and 70 diastolic. The blood Wassermann reaction was negative. The coagulation time of the blood was twelve minutes. The blood examination on admission revealed 40 per cent hemoglobin and 2,500,000 red cells. Two years later, shortly before death, the hemoglobin percentage was 20 and the red blood cells numbered 790,000. The white cells numbered 4,800 with 59 per cent polymorphonuclears and 41 per cent mononuclears. There was moderate poikilocytosis, but there was no macrocytes. The patient continued to have frequent severe nosebleeds in spite of all therapy and finally succumbed, Feb 11, 1921, to the effect of a severe anemia. Necropsy revealed numerous gummas of the liver with syphilitic cirrhosis. The heart was greatly enlarged, weighing 680 Gm. The right auricle and ventricle

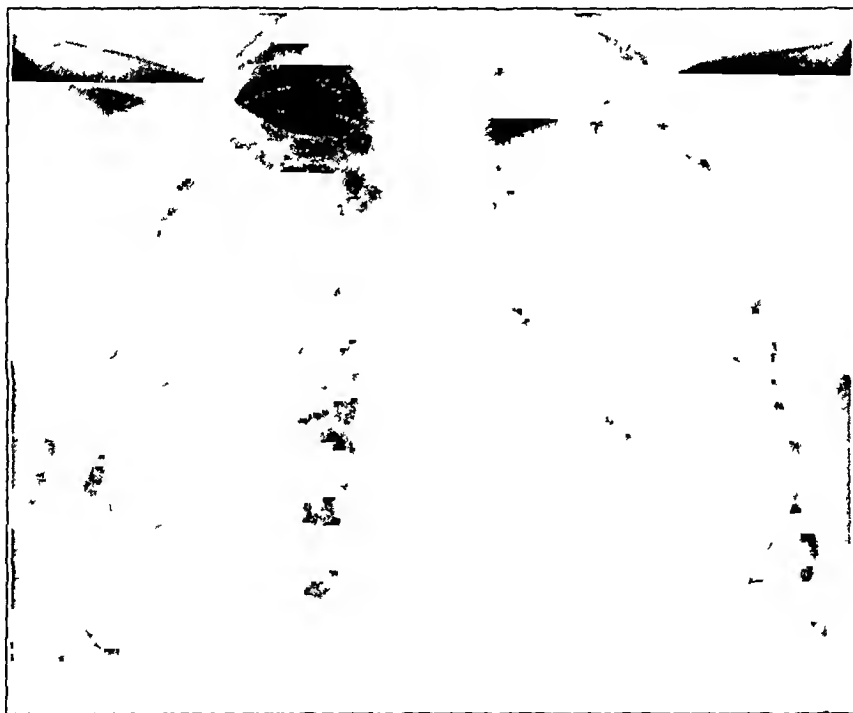


Fig 3 (case 4) —Heart showing enlargement and mitral configuration

were strikingly dilated, while the left auricle and ventricle showed moderate dilatation. The right ventricle measured 4 mm, the left 12 mm in thickness. The valves were normal. There was considerable "tigering" of the myocardium. The coronary arteries showed scattered atherosclerotic plaques. The kidneys together weighed 280 Gm. Their surfaces were smooth and their cortices wide. The lungs showed moderate emphysema.

CASE 4—E. H., a man, aged 40, was admitted to Montefiore Hospital, March 17, 1925, complaining of weakness and loss of weight of one year's duration. Physical examination revealed a mass on the inner aspect of the right ilium, marked yellowish pallor, and signs of funicular myelitis. The hemoglobin was 18 per cent, the red cells numbered 960,000. There were no nucleated forms or macrocytes. There were 11,000 white blood cells, with 83 per cent polymorphonuclears, 12 per cent lymphocytes, 2 per cent mononuclears and 3 per cent myelocytes. The heart was slightly enlarged to the left with an apical systolic murmur. The blood pressure was 100 systolic and 70 diastolic. The patient died, Aug 7, 1925. Necropsy revealed a large retroperitoneal sarcoma. The heart weighed 400 Gm.

There was much epicardial fat. The right auricle and ventricle were dilated. The right ventricle measured 5 mm and the left 10 mm in thickness. The valves were normal.

Dilatation of the heart in severe anemia is due most probably to the deficient oxygen supply to the cardiac muscle. In another connection Lewis<sup>15</sup> has suggested that an inadequate blood supply to the heart will cause it to dilate. Ludke and Schuller<sup>16</sup> were able to demonstrate cardiac dilatation in dogs that were subjected to experimental anemia. The diastolic murmur that is heard apparently only in patients with far advanced anemia whose hearts are enlarged is caused most probably by the accompanying stretching and relaxation of the aortic ring. The origin of a presystolic murmur is less readily understood. The observations of Fahr and Ronzone,<sup>17</sup> while not absolutely conclusive, suggest a greatly increased minute volume flow as well as an accelerated blood velocity as a compensatory phenomenon to the lessened oxygen carrying power of the blood in severe anemias. It is readily conceivable that this might increase the work of the heart to a degree sufficient to cause hypertrophy of the ventricular chambers. The relative frequency of marked right ventricular dilatation in our series of cases is worthy of note but not readily explained.

#### SUMMARY

Cardiac dilatation, often accompanied by cardiac hypertrophy, is a common finding in patients with severe anemias. Diastolic murmurs resembling those of aortic insufficiency are heard in about 10 per cent of patients with pernicious anemia. These are caused not by organic valvular disease but by a relative insufficiency of the aortic valve. In a smaller number of anemic patients presystolic murmurs may be present in the absence of mitral stenosis. In patients with severe anemia the presence of cardiac enlargement, a nutral configuration of the heart, and a diastolic or presystolic murmur does not warrant the diagnosis of organic valvular disease.

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15 Lewis, T, and Drury, A. N. Observations Relating to Arteriovenous Aneurysm, *Heart* **10** 301, 1923.

16 Ludke, H, and Schuller, L. Ueber die Wirkung experimenteller Anamien auf die Herzgrosse, *Deutsches Arch f klin Med* **101** 512, 1910.

17 Fahr, G. E, and Ronzone, E. Circulatory Compensation for Deficient Oxygen Carrying Capacity of the Blood in Severe Anemias, *Arch Int Med* **29** 331 (March) 1922.

# SICKLE CELL ANEMIA

REPORT OF A CASE GREATLY IMPROVED BY SPLENECTOMY  
EXPERIMENTAL STUDY OF SICKLE CELL FORMATION \*

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The term "sickle cell anemia" is used to designate two conditions (1) a hereditary predisposition to anemia occurring only in the negro race and characterized by the development of a crescentic distortion of the red corpuscles under certain conditions, and (2) a chronic, severe anemia affecting only negroes with this predisposition, characterized by remissions and exacerbations, hemolytic jaundice, episodes of abdominal pain, joint pains without inflammation and a tendency to ulcer of the leg

In 1910 Herrick<sup>1</sup> reported a case of a negro who had jaundice, a history of ulcer of the leg, leukocytosis and severe anemia associated with the occurrence of crescentic red corpuscles in the stained and wet smears of the blood. Some of the crescentic poikilocytes were nucleated

Washburn<sup>2</sup> reported the second case with essentially the same clinical picture, and Cook and Myer,<sup>3</sup> the third. Cook and Myer believed that the condition constitutes a clinical entity, and that its incidence is familial

Emmel<sup>4</sup> published separately a study of the third case, reporting that the number of sickle cells in sealed wet smears of the patient's blood increased on standing, that during remissions when stained smears showed no sickles, such forms appeared in sealed wet smears, and that sickles developed in such preparations of the blood of the patient's

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\* From the Laboratory of Surgical Pathology, Indiana University School of Medicine

1 Herrick, J B. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch Int Med **6** 517 (Nov) 1910

2 Washburn, R E. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Virginia M Semi-Month **15** 490 (Feb) 1911

3 Cook, J E, and Myer, J. Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcers, Arch Int Med **16** 644 (Oct) 1915

4 Emmel, V E. A Study of Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch Int Med **20** 586 (Oct) 1917

clinically healthy father Emmel noted evidence of phagocytosis of the corpuscles by large mononuclear cells in the stained smears. He found no nucleated sickle cells, and concluded that sickle cells are formed in the circulating blood. He believed that the sickle distortion, which he regarded as specific for this type of anemia, was the result of an accentuation of the factors normally involved in the transformation of the original spherical erythrocytes into biconcave disks.

Mason,<sup>5</sup> reporting the fourth case, first used the term "sickle cell anemia."

Sydenstricker, Mulheim and Houseal<sup>6</sup> added cases five and six, the latter with an autopsy report. The nonfatal case was the first in which the spleen was enlarged. The occurrence of nucleated sickle cells in the peripheral blood was again affirmed. Attacks of abdominal pain were stressed as a prominent symptom and related to splenic pathologic change. Sickle cells were found in the tissue sections of the case which came to autopsy, and were particularly numerous in smears of the bone marrow. The manner of fixation was not stated explicitly, but liquor formaldehydi was mentioned with reference to one tissue. The authors concluded that sickle cells are preformed in the bone marrow, and that the anemia is hemolytic.

Huck,<sup>7</sup> reporting cases seven and eight, stated for the first time that sickle cells in wet smear cultures revert to the circular form after a variable period of time. Washed corpuscles suspended in physiologic sodium chloride and citrate solution became sickle cells as readily as in the presence of serum. Phagocytosis of red cells by large mononuclears was observed in stained smears. Huck submitted brief notes of symptoms and blood observations on twelve other persons, eleven of whom belonged to one family. Sickle cells were found in stained smears of the blood of those with impaired health and anemia. In those with slight or no symptoms and practically normal red cell counts, the sickle cell tendency was proved by observation of wet smear cultures. The completeness of the sickle cell formation was roughly proportional to the severity of the symptoms. Huck, on this evidence, introduced the concept of latent sickle cell anemia. A study of the families convinced him that the disease is inherited as a dominant mendelian trait.

In 1924 Sydenstricker<sup>8</sup> summarized observations on his series of eighty cases distributed among ten families. In the entire series seventy-

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5 Mason, V. R. Sickle Cell Anemia, *J. A. M. A.* **79** 1318 (Oct. 14) 1922.

6 Sydenstricker, V. P., Mulheim, W. A., and Houseal, R. W. Sickle Cell Anemia. Report of Two Cases in Children with Necropsy in One Case, *Am. J. Dis. Child.* **26** 132 (Aug.) 1923.

7 Huck, J. G. Sickle Cell Anemia, *Bull. Johns Hopkins Hosp.* **34** 335 (Oct.) 1923.

8 Sydenstricker, V. P. Further Observations on Sickle Cell Anemia, *J. A. M. A.* **83** 12 (July 5) 1924.

one patients had latent sickle cell anemia, and eleven of these had a palpable spleen and five had ulcer of the leg. In the patients with active anemia, the liver was regularly enlarged, the spleen was palpable only when there was a history of malaria, and the legs showed ulcers, or scars of ulcers, and edema. Red cell resistance was increased, bilirubinemia was marked, and urobilin was increased in the urine and stools. The urine did not contain bile. Phagocytosis was observed in stained blood smears of patients with active and latent anemia and wet smear cultures showed sickle cell formation with phagocytosis of the sickle cells. The statistical evidence of hereditary transmission was reinforced by finding sickle cells in the blood from the umbilical cord in two patients. The phenomenon of auto-agglutination was observed in four patients. The summary of five autopsies included the following points: enlarged liver with pigment and degeneration, atrophic spleen with decrease of pulp and follicles, increase of trabecular tissue, fine pigment, deposits of iron containing pigment, recent and old infarcts and overfilling with blood irregularly distributed, hyperplastic bone marrow, and the lesions of intercurrent infections. Sydenstricker concluded that the disease is probably a hereditary defect in the spleen and blood-forming tissues resulting in an abnormality of the red cells predisposing them to hemolysis and phagocytosis, and that when anemia is present it is caused by an activation of hemolysis by factors innocuous to normal persons.

Graham,<sup>9</sup> reporting the ninth case, stressed the fact that sickle cell formation in wet smear cultures is inconstant. Slides prepared in the same way and at the same time yielded both positive and negative results. The case came to autopsy and Graham was able to report that the red corpuscles of the tissues fixed in liquor formaldehydi were all sickle cells, but that those of the tissues fixed in Zenker's solution were normal in shape. Graham regarded the latent phase of the disease as a 'status hemicus'. The excitant provoking the active phase he considered to be probably a metabolic disturbance or an infection.

Moser and Shaw<sup>10</sup> reported the tenth case, the first in a "northern" negro. The patient had never been out of Nebraska, and his family had lived in the North for several generations. The authors found that the blood serum of their patient did not hemolyze normal red cells.

The subject of Anderson's report,<sup>11</sup> the eleventh case, was a Pennsylvania negro. Anderson confirmed Graham's experience of the capriciousness of sickle cell formation in wet smear cultures.

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9 Graham, G. S. A Case of Sickle Cell Anemia with Necropsy, *Arch. Int. Med.* **34** 778 (Dec.) 1924.

10 Moser, A. R., and Shaw, W. J. Sickle Cell Anemia in a Northern Negro, *J. A. M. A.* **84** 507 (Feb. 14) 1925.

11 Anderson, H. B. Sickle Cell Anemia. Report of an Active Case, *Am. J. M. Sc.* **171** 641 (May) 1926.

Hamilton<sup>12</sup> reported the twelfth case which was complicated by gallstones, for which laparotomy had been performed, and Browne<sup>13</sup> reported the thirteenth

The case presented here is the fourteenth to be reported in detail, the first to be reported from Indiana, and the first to be reported in which the patient was treated by splenectomy

#### REPORT OF CASE

*History*—Curtis C., colored, aged 4, was brought to the James Whitcomb Riley Hospital, Dec 23, 1925. His mother said that for months he had been tired and sleepy. During this time he had had frequent attacks of epistaxis and had complained of headache, he had also had intermittent attacks of epigastric pain associated with vomiting. His health had never been good. He had had bronchopneumonia at the age of 8 months, rheumatism with swelling of the elbow joints some months later, pertussis at the age of 1 year, and both measles and influenza at the age of 3. The mother was not in good health. The father and three sisters were in good health. The maternal grandfather died of heart trouble. The maternal grandmother was living but afflicted with tuberculosis. The paternal grandparents were in good health. There was no history of jaundice or ulcer of the leg.

*Examination*—The patient was fairly well nourished. The sclera showed a greenish color. The mucous membranes were pale, the teeth carious, the tonsils small but inflamed. The lymph glands of the neck were moderately enlarged, of the axillary and inguinal regions, slightly enlarged. On the left side, lung resonance was impaired, moist râles were heard, and a friction rub was present in the axillary line at interspaces 6, 7 and 8. The right lung was apparently normal. The maximal impulse was in the nipple line at interspace 5, the apex beat, 2 cm lateral to the nipple line. A loud blowing systolic murmur, heard best at the apex, was transmitted to the axilla. The second sound was loud and snappy. The abdomen was distended and tympanic on the right, on the left, it was occupied by the spleen which extended to the crest of the ilium. The spleen was firm and not tender. Its notch was distinctly felt. The liver was palpable 2 fingerbreadths below the costal border. The rectal temperature varied daily between 98.6 and 100.5 F, the pulse rate between 90 and 120. A febrile crisis, reaching a peak of 104.5 F, occupied a period of five days and was unattended by signs suggestive of its cause. (Laboratory data susceptible of tabulation are given in tables 1 and 2.) The urine was dark but normal to the ordinary tests, including the shake test for bile. The stool was normal except for its high content of urobilin, there were no ova, parasites or undigested food. The blood Wassermann reaction was negative twice, blood culture was negative, and auto-agglutination was negative. The whole blood had a cholesterol content of 81 mg per hundred cubic centimeters, as estimated by the method of Leiboff. The coagulation time was seven minutes and the bleeding time was two minutes. Wet smears of the fresh blood contained a few more or less crescentic poikilocytes. Typical sickle cells developed in sealed wet smears in twenty-four hours at room temperature and reverted to a circular form in two weeks.

*Operation and Result*—The patient's symptoms were all explicable on the ground of severe anemia, except for the attacks of epigastric pain which we attributed to pathologic change in the spleen. The laboratory data confirmed the clinical diagnosis of severe anemia and established the presence of acholuric

12 Hamilton, J. F. A Case of Sickle Cell Anemia, U. S. Veterans' Bureau M. Bull. 2:497 (May) 1926.

13 Browne, Earl Z. Sickle Cell Anemia, M. Clin. N. Amer. 9:1191 (Jan) 1926.

jaundice of hemolytic origin. The tremendous rate of blood destruction was revealed by the enormous output of urobilinogen and urobilin (estimated together). The febrile course and leukocytosis were held to establish the presence of an infection which might be either etiologic or intercurrent in its significance. The high leukocyte counts, the high percentage of reticulocytes and the presence in the circulating blood of nucleated red cells were taken to indicate hyperfunction of the hematopoietic system, presumably compensatory. Thus far, the case was considered typical of acquired hemolytic jaundice. However, one datum, the increased resistance of the red cells, was inconsistent with that diagnosis. Finally, the demonstration of sickle cells was held to establish the diagnosis of active sickle cell anemia.<sup>14</sup>

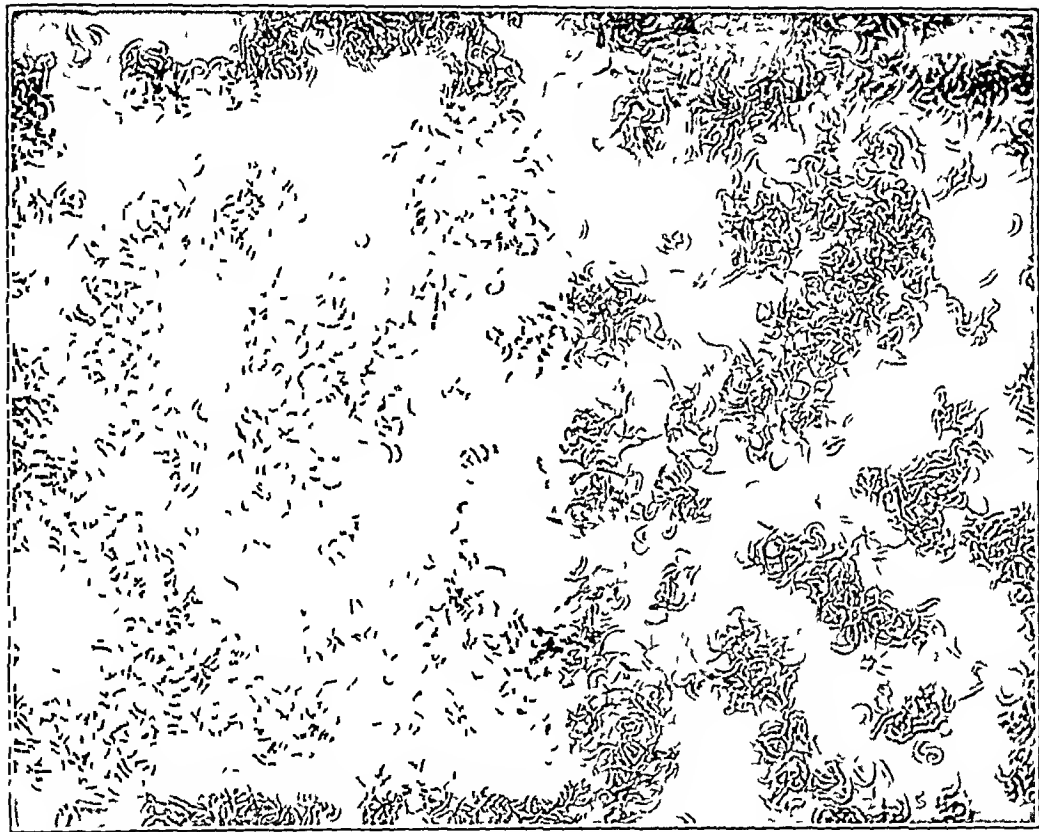


Fig 1—A wet smear culture of the patient's blood forty-eight hours after preparation. Practically all of the red corpuscles are sickle shaped. The apparent colonization of the corpuscles around granular areas has not been reported previously.

Sydenstricker<sup>15</sup> and Huck had suggested that splenectomy might be beneficial in sickle cell anemia. We considered it especially indicated in this case because of the conditions stated in the foregoing and because the patient's red cell count was steadily falling. An effort to find a compatible donor for a preliminary blood transfusion was unsuccessful, and the patient's sole therapy was splenectomy.<sup>16</sup>

14 The assistance of Dr J O Ritchey and of Dr J Don Miller, Department of Medicine, Indiana University School of Medicine, is acknowledged.

15 Sydenstricker, V P. Sickle Cell Anemia, *South M J* **17** 177 (March) 1924. The opinion of J G Huck was given in his discussion of this paper.

16 The operation was performed by Dr Murray N Hadley, Department of Surgery, Indiana University School of Medicine.

Immediate convalescence was uneventful. Clinical improvement later was rapid. The tables show that the red cell count rapidly increased and that the output of urobilinogen-urobilin rapidly decreased. For one month after operation it was impossible to detect sickle cells in sealed wet smears prepared exactly as before operation. Later they could be found as regularly as before operation. One fragility test after operation showed a decrease of resistance. A subsequent test again showed increased resistance which, however, was at a level nearer the normal than the preoperative values. The patient at the present time is symptomatically well and shows no sign of icterus. However, he still has the sickle cell trait.

*Pathologic Changes in the Spleen*—After removal and in the fresh condition the spleen was about three times the normal adult size. After twenty-four hours of fixation in formaldehyde, the organ measured 14 cm from pole to pole.

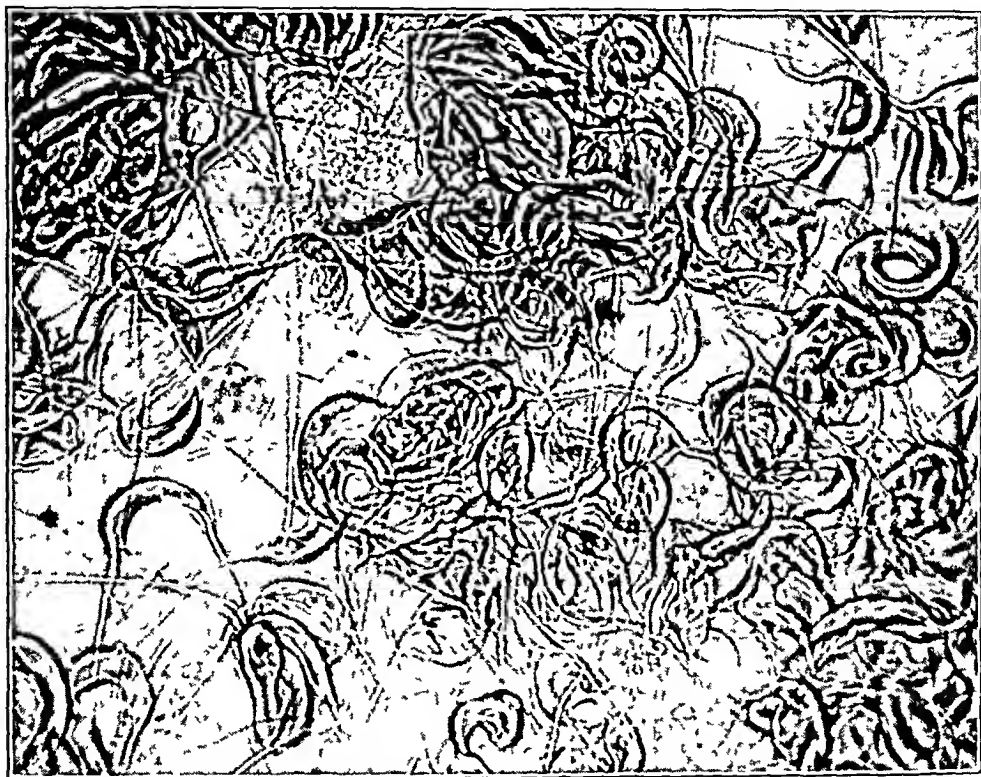


Fig 2—An oil immersion view of the specimen represented in figure 1. Under working conditions, practically all the filaments could be traced to the horns of sickle shaped corpuscles.

In the fresh condition the spleen was soft and a dark purplish color. The surface was coarsely pebbled, and the margins were more obtusely rounded than normally, giving the impression of turgidity. The vessels of the hilum presented no calcifications, thrombi or abnormal thickenings.

The spleen cut with less than normal resistance. The capsule was about twice the normal thickness, and there were opaque patches of still greater thickness. The parenchyma was extremely soft and of a dark red color. Malpighian bodies were not visible.

Under aseptic conditions, a sample of the pulp was taken for bacteriologic culture, and two blocks were cut for histologic examination. One of the blocks was fixed in 4 per cent formaldehyde and the other in Zenker's solution. Both were dropped into the fixing solutions within ten minutes of the delivery of the organ from the abdomen.

The tissue culture yielded a green-producing streptococcus in pure culture. The following microscopic observations were made on the tissue fixed in formaldehyde except where it is explicitly stated otherwise. Hematoxylin and eosin preparations showed a slight thickening of the capsule but no increase in trabecular tissue. On the contrary, the trabeculae were spaced farther apart than in the normal organ. Lymphoid follicles were almost totally lacking, and there was a general paucity of lymphocytes. The tissue was overstuffed

TABLE 1—*Blood Cell Counts, Hemoglobin Determinations, Differential Formulas and Fragility Tests Before and After Splenectomy*

Date	Red Blood Cells	Hemoglobin	Color Index	White Blood Cells	Lymphocytes	Large Mononuclear Transitionals	Neutrophilic Polymorphonuclears	Eosinophilic Polymorphonuclears	Basophilic Polymorphonuclears	Nucleated Red Cells per 100 White Blood Cells	Reticuloocytes, per Cent	Platelets	Limits of Hemolysis Sodium Chloride, per Cent	
													Patient	Control
12/24	2,110,000	30	0.72	13,000	40	5.5	45.5	0.5	1.5	7			0.32-0.20	0.48-0.40
12/30	2,000,000	30	0.75	12,000	42	7.0	49	1.0	1.0	7			0.30-0.22	
1/4	1,850,000			18,000	40	5.0	54	1.0	0	11	19			
1/10	1,936,000											253,000	0.30-0.20	0.50-0.40
1/15														
1/19	Splenectomy													
1/20				28,000										
1/24	2,256,000			16,400								160,000		
2/8	4,072,000	35	0.48	17,000								224,000	0.60-0.50	
2/21	4,432,000	40	0.45	25,000									0.40-0.30	

TABLE 2—*Bilirubin in the Blood Serum and Urobilin in the Excreta Before and After Splenectomy\**

Date	Serum Bilirubin (Van den Bergh Reaction)				Urobilin Excretion†	
	Direct		Indirect		Urine, Mg per 24 Hours	Stool, Mg per 24 Hours
	1 Minute	1 Hour	Mg per Liter	Units		
1/1	—	+	13.4	2.7		
1/8	—	+	14.5	2.9		
1/17					40#	
1/18					137	18,200¶
1/19					101	
1/19	Splenectomy					
1/27						623
2/2					58	607
2/3					39	22
2/7					18	379
2/8	—	±	18	0.3	41	245
2/9					38	
2/10						205

\* All chemical analyses were made by Dr. R. N. Harger, Department of Biochemistry, Indiana University School of Medicine.

† In the method of Elman and McMasters, Urobilin Physiology and Pathology, Quantitative Determination of Urobilin, J. Exper. Med. 41:503 (April) 1925, which was used, the urobilinogen is converted into urobilin, and both are therefore estimated with each other. A nephelometer was used in place of a color comparator box. The acriflavine was purchased from Coleman and Bell.

# This value was obtained on a stale specimen.

¶ This value was obtained for a bulky specimen which is thought to have represented two days' excretion.

with red corpuscles, and pulp cells were numerous only in residual islands remote from the sinusoids. The sinusoids presented an empty appearance except for adherent large white cells within the lumina. The red corpuscles were strikingly elongated and even filiform. Areas of coarse brown granules were observed in and near some of the coarser trabeculae and in the capsule.

This pigment gave the Prussian blue reaction for iron. There was no trace of finely granular pigment or of red cell phagocytosis.

Polychrome methylene blue and eosin preparations showed diffusely scattered cells resembling eosinophilic myelocytes. The red cells, which took a deep polychrome stain, were packed in largest numbers in the perisinusoidal zones, which were definitely delimited from the surrounding reticulum.

The tissue fixed in Zenker's solution cut badly because of great friability. However, several sections showed definitely that the red cells were normal in appearance and not elongated.

Stained smears were made of red cells triturated out of unblocked tissue fixed in 4 per cent formaldehyde. These red cells were all elongated, and many were crescentic.

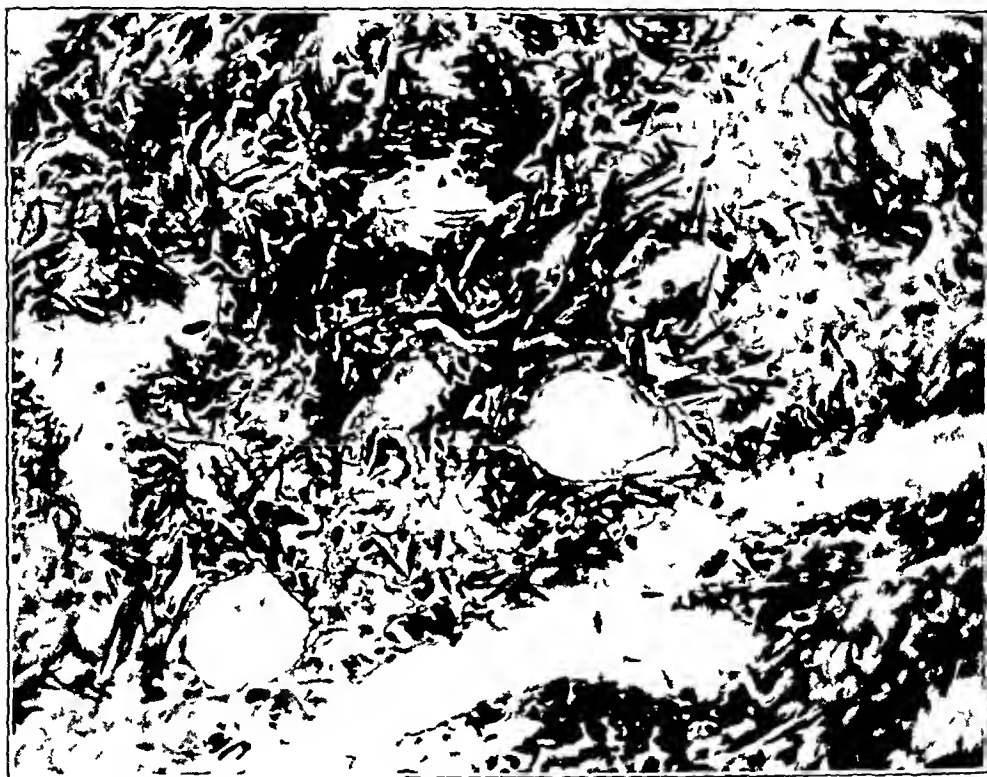


Fig 3—Section of the spleen stained by the Gram-Weigert method. The photomicrograph was made with light filtered to increase the contrast between the tissue and the red corpuscles, which were stained deep purple. The rod-shaped, intensely black objects represent elongated red corpuscles lying with their long axes in the plane of the section. The small round and elliptical black objects represent cross and oblique sections of elongated red corpuscles.

#### MECHANISM OF THE SICKLE DISTORTION

Neither our patient nor any member of his family had definite sickle cells in their circulating blood as far as we could determine by examination of stained or fresh wet smears. Our patient was shown to belong to the sickle cell anemia group by the demonstration of sickle cells in sealed wet smears kept at room temperature for twenty-four hours. The patient's mother and two of his sisters were shown to have "latent sickle cell anemia."

It is apparent from these facts, as well as from published reports, that the sickle cell is not a distorted cell produced as such by the erythropoietic tissue. On the other hand, it is indistinguishable from normal cells until acted on by unknown factors. In undertaking an investigation of these factors, we hoped to gain some insight into the nature of the fundamental defect of the cells and the mechanism of the production of anemia.

Previous experiments with sickle cells have yielded the following data:

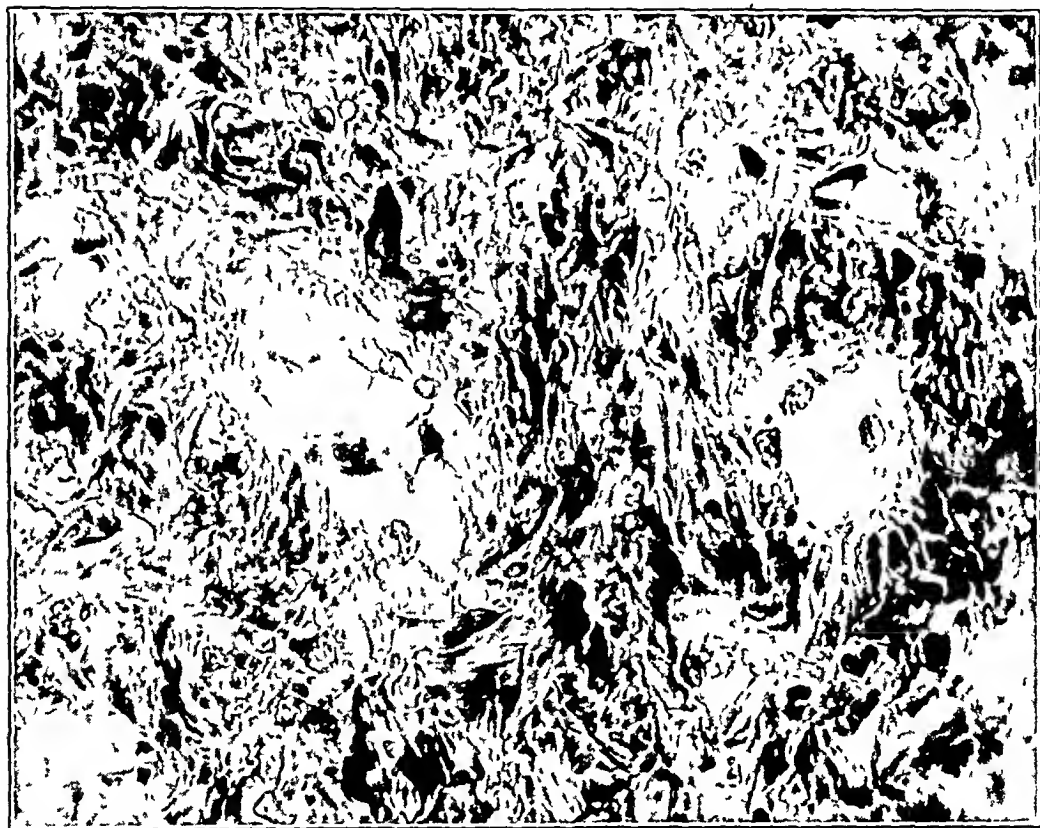


Fig. 4—Section of the spleen stained with polychrome methylene blue and eosin, showing the concentration of the elongated red corpuscles in perisinusoidal zones which are more or less delimited from the surrounding reticulum. Large cells are shown adherent to the sinusoidal endothelium.

- 1 Sickle cell formation is retarded by cold and accelerated by heat.<sup>6</sup>
- 2 Sickle cell formation is independent of exposure to light, although return to spherical shape is more rapid in the dark.<sup>7</sup>
- 3 Serum is not essential for sickle cell formation, as the susceptible cells undergo the distortion in saline or citrate suspension.<sup>17</sup>

<sup>17</sup> Huck, J. G. (footnote 7). Sydenstricker, Mulherin and Houscal reported that serum is essential. Their negative result cannot be as conclusive as the positive results obtained by Huck which were also confirmed by our own observations.

4 Susceptible cells, washed, become sickle cells in normal serum of the same blood type<sup>18</sup>

5 Normal cells do not become sickle cells by the action of the serum of a person whose blood contains sickle cells<sup>18</sup>

6 Bile pigment and bile salts accelerate sickle cell formation<sup>6</sup>

7 Phagocytosis of sickle cells by large mononuclears occurs in vitro<sup>6</sup>

8 Large mononuclears of a person whose blood contains sickle cells do not phagocytize normal red cells<sup>6</sup>

9 Production of sickle cells is inconstant in preparations made under identical conditions<sup>19</sup>

10 Red cells of tissue of affected subjects, fixed in formaldehyde, are sickle cells, when Zenker's solution is used, sickle cells are not present<sup>20</sup>

In the course of preliminary experiments testing the effect of formaldehyde, we found that the patient's corpuscles sedimented by gravity from a neutral citrated saline suspension and drawn from the bottom of a serum tube with a pipet showed a considerable percentage of sickle cells. Samples drawn from the same suspension after agitation showed no sickle cells.

The most obvious difference between corpuscles which had settled at the bottom of a serum tube, and corpuscles which had recently been agitated was oxygen tension, if one assumes that the corpuscles and perhaps the leukocytes continued a metabolism which rendered their environment progressively poorer in oxygen. As the product of such an assumed metabolism would be carbon dioxide, we were obliged to take into consideration (1) the presence of carbon dioxide, (2) a shifting in the hydrogen ion concentration and (3) deprivation of oxygen.

Acting on these considerations, we arranged a series of experiments in which hanging drops of the corpuscle suspension, inverted over a gas chamber provided with inlet and outlet tubes, were observed with a 4 mm objective. Various gases were passed through the chamber. Figure 6 shows in diagram the arrangement of the apparatus.

#### EFFECT OF VARIOUS GASES ON CORPUSCLES IN CITRATE-SALINE SUSPENSION

Carbon dioxide was passed through the gas chamber in a gentle stream after thorough saturation with water vapor at room temperature. Sickle formation of the patient's corpuscles occurred in less than two

18 Huck, J. G. (footnote 7), Sydenstricker (footnote 6)

19 Graham, G. S. (footnote 9), Anderson, H. B. (footnote 11). Also confirmed by our own observations.

20 Graham, G. S. (footnote 9). Also confirmed by our own observations.

minutes Nitrous oxide and hydrogen each caused identical reactions in from two to five minutes Nitrogen failed to cause sickle formation in the unaltered (neutral) suspension Ethylene brought about perfect sickle production on its first trial On subsequent trials, its effect on the corpuscles of the unaltered (neutral) suspension was inconstant

Oxygen and carbon dioxide were found to be absent, as impurities, in samples of the aforementioned gases in amounts which could be detected by the Haldane gas analysis apparatus All the gases were examined for the presence of volatile substances of acid nature by bubbling them through freshly distilled water for thirty minutes A shift



Fig 5—Stained smear of the red blood corpuscles triturated out of spleen tissue fixed in formaldehyde

in the hydrogen ion concentration of the water was not detected in any case by the colorimetric test

#### REVERSIBILITY OF THE SICKLE CELL DISTORTION

The admission of pure oxygen to the gas chamber after the sickle cell formation by carbon dioxide instantly brought the cells to a discoid state This reversal was equally prompt after exposure to all the gases causing sickle cell formation

Carbon monoxide was passed through the gas chamber The corpuscles in equilibrium with carbon monoxide retained their discoid contour Passing carbon dioxide after exposure to carbon monoxide

brought about sickle cell formation in four minutes. A new exposure to carbon monoxide caused instant reversal to the discoid form. The experiment was repeated, starting with carbon dioxide, and a long series of reversals was carried out.

#### INTERPRETATION OF DATA SO FAR REPORTED

The most significant common property of carbon dioxide, hydrogen and nitrous oxide is that they contain no oxygen which is chemically available under the conditions of the experiment. The most obvious conclusion to be drawn from the fact that these three gases induced sickle cell formation is that the distortion occurs as a result of oxygen asphyxia of the susceptible corpuscles.

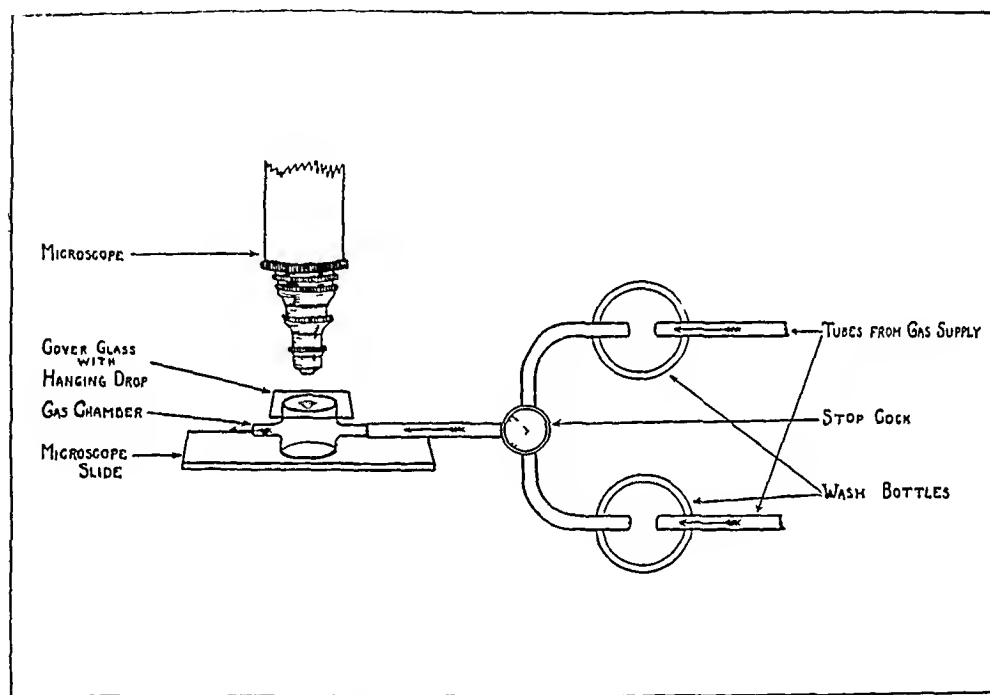


Fig 6—Arrangement of the apparatus used to test the effect of gases on red corpuscles

The validity of this conclusion apparently is threatened by the fact that ethylene failed to induce sickle cell formation constantly, and that nitrogen failed entirely when the corpuscles were tested in the original neutral citrated saline suspension. That this discrepancy is only apparent will be shown in the section on the influence of hydrogen ion concentration on the asphyxia reaction.

The behavior of the corpuscles toward oxygen greatly strengthens the conclusion stated in the foregoing and shows that sickle cell formation is a reversible phenomenon depending on the oxygen tension of the medium in which the cells are suspended. In the presence of oxygen, the discoid form is stable, in its absence the distorted form is stable.

The behavior of the corpuscles toward carbon monoxide calls attention to a second property common to the gases causing sickle cell production. None of them forms as definite or as stable a compound with hemoglobin as do oxygen and carbon monoxide. The previously stated conclusion may therefore be expanded into the following hypothesis: Sickle cell formation is a reversible phenomenon depending on the free or combined state of the hemoglobin of the susceptible corpuscles. When the hemoglobin is in the combined state, the discoid form is stable, when in the uncombined state, the distorted form is stable<sup>21</sup>. The behavior of the susceptible corpuscles toward oxygen asphyxia thus constitutes a special application of a hypothesis correlating contour with the state of the hemoglobin.

#### DEGREE OF SENSITIVENESS TO OXYGEN

In all the foregoing experiments, pure gases were used to effect the reversal to discoid form. In order to determine the partial pressure of oxygen rendering the sickle form unstable, mixtures of carbon dioxide and oxygen were prepared, passed through the gas chamber and then analyzed in the Haldane apparatus.

A mixture proving by analysis to be 6.4 per cent oxygen failed to cause any typical sickle cell production during ten minutes of exposure. A mixture with 3.5 per cent oxygen caused about 50 per cent of the corpuscles to assume the sickle form in five minutes and about 90 per cent of them in eight minutes.

We concluded that the maximum concentration of oxygen in which the sickle form is stable is about 6 per cent, which corresponds to a partial pressure of 45 mm. of mercury.

#### ASPHYXIA REACTION OF CORPUSCLES OF MEMBERS OF PATIENT'S FAMILY AND OF CONTROLS

The corpuscles of the patient's mother and of two of his sisters showed the sickle reaction when tested in neutral citrated saline suspension with carbon dioxide. The corpuscles of the two sisters showed the sickle reaction when tested in neutral suspension with hydrogen and nitrous oxide.

These relatives of the patient were apparently well. None had splenomegaly or anemia, and none showed sickle cells in stained smears or wet smear cultures, yet their red corpuscles were clearly demon-

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<sup>21</sup> A possible objection to our hypothesis may be based on the known relative stability of carbonyl hemoglobin. It must be remembered, however, that the corpuscles were in a thin film of suspension, and that the carbon dioxide was moving in a stream, carrying out of the gas chamber all traces of gaseous carbon monoxide. The conditions were thus proper for the progressive completion of an equilibrium reaction in accordance with the law of mass action.

strated to have the fundamental defect which renders them susceptible to distortion when subjected to oxygen asphyxia

That the sickle distortion as an asphyxia reaction is specific for the corpuscles of certain family groups of negroes is indicated by the negative results obtained on examining the corpuscles of numerous controls by the technic which has been described. The negative controls consisted of the father and paternal grandmother of the patient, negro children in the hospital with ailments unrelated to anemia, a patient with pernicious anemia and numerous healthy white subjects.

The technic used in the foregoing experiments, simplified by omitting provision for two gases, is proposed as a reliable and rapid diagnostic test for sickle cell anemia. A drop of the subject's blood in physiologic sodium chloride, a gas chamber, a microscope and a cylinder of carbon dioxide, which is available in most hospitals, are all that is necessary. Reversibility of the distortion can readily be demonstrated by admitting a little air to the hanging drop.

#### INFLUENCE OF HYDROGEN ION CONCENTRATION IN THE ASPHYXIA REACTION

In a previous section it was stated that the patient's corpuscles in neutral suspension failed to change to a sickle cell form when tested with nitrogen, and that they sometimes failed when tested with ethylene. Reference to table 3 will show that in a neutral suspension, the corpus-

TABLE 3—*Reactions of Corpuscles of Various Persons to Pure Gases in Equilibrium with Hanging Drops of Corpuscle Suspension*

Subject	Carbon Dioxide, Neutral	Hydrogen, Neutral	Nitrous Oxide		Ethylene		Nitrogen	
			Neutral	Acid	Neutral	Acid	Neutral	Acid
Patient	+	+	+	+	±	+	—	+
Mother	+	—	—	+	—	+	—	—
Sister, 2 years	+	+	+	+	—	+	—	—
Sister, 9 months	+	+	+	+	—	+	—	—
Father	—	—	—	—	—	—	—	—
Paternal grandmother	—	—	—	—	—	—	—	—
Normals	—	—	—	—	—	—	—	—
Pernicious anemia	—	—	—	—	—	—	—	—

\* The sign + means that sickling occurred, —, that sickling did not occur, ±, that sickling occurred on some trials and did not occur on others, a blank ( ) space, that no test was made. In the columns headed "Neutral" are the reactions of the corpuscles in an approximately neutral citrated 0.8 per cent sodium chloride solution. In the columns headed "Acid" are the reactions of corpuscles suspended in the same medium altered by the addition of an equal volume of buffer solution of  $pH$  6.8.

cles of the patient's mother and of two of his sisters failed to assume a sickle cell shape with ethylene, and that in neutral suspension the corpuscles of the mother failed to assume this form with nitrous oxide.

This anomalous behavior of susceptible corpuscles toward oxygen-free gases was taken to indicate the participation of an additional factor in the reaction. The fact that carbon dioxide, the only gas of the series which altered the hydrogen ion concentration of the aqueous medium

invariably caused sickle cell formation led to the suspicion that certain conditions of hydrogen ion concentration are prerequisite to the reaction

Portions of the corpuscle suspensions of the patient, the mother and the two sisters were mixed with equal volumes of a buffer solution of  $p_H$  6.8. These acidified suspensions were then tested with the aforementioned gases which had produced no sickle cell formation in the corresponding neutral suspensions. Sickle cells occurred in every instance within five minutes after starting the stream of gas, and was constant on repeated trials.

Previous acidification was not necessary in the reaction of the corpuscles of the patient with hydrogen and nitrous oxide, neither was it necessary in the reaction of the corpuscles of the two sisters with nitrous oxide, nor in the reaction of the patient's corpuscles with ethylene on occasional trials.

As these inconsistencies were neither constant nor significantly associated with any other properties of the gases, it was considered that they arose from differences in the sensitiveness to asphyxia of corpuscles from various persons and from accidental shifts in the hydrogen ion concentration.

#### RANGE OF HYDROGEN ION CONCENTRATIONS WITHIN WHICH SICKLE CELL FORMATION OCCURS IN ASPHYXIA

As a check on the results already obtained, it was considered advisable to determine the limits of hydrogen ion concentration within which sickle cell formation occurs in oxygen asphyxia. Ethylene was used in this series of experiments because more often than any of the other gases it failed to cause sickle cell formation of susceptible corpuscles in neutral suspension.

Two methods of altering the hydrogen ion concentration of the suspension were employed. First, equal drops of the citrated saline suspension and the buffer solution were mixed on cover slips which were then inverted over the gas chamber. After several minutes of observation to make sure that sickle cell formation was not induced by shift of the hydrogen ion concentration alone, the ethylene was turned on. Second, one-hundredth cubic centimeter portions of a thick suspension of washed corpuscles were mixed in small test tubes with 1 cc portions of buffer solutions. Small drops of these suspensions were then mounted and treated as before.

We found it possible to measure roughly the relative suitability of the various suspensions to form sickle cells by estimating in percentage the extent of the reactions as judged by the numbers of corpuscles that had assumed the sickle cell shape and by the completeness of the distortion of individual corpuscles at the expiration of five minute periods.

Sickle cell formation generally occurred more quickly at the edges of the drops, and in the less suitable solutions, only there. In two series of trials with the patient's corpuscles, by the method of suspension, we kept separate data of the reaction at the edge and at the center

The results shown graphically in figures 7 and 8 are consistent in general. From the point of beginning hemolysis in the more acid suspensions, the ability to undergo sickle cell formation rapidly increases with decreasing acidity to a maximum which is maintained over a wide range, and begins rapidly to decrease with increasing alkalinity at a point not far from neutrality

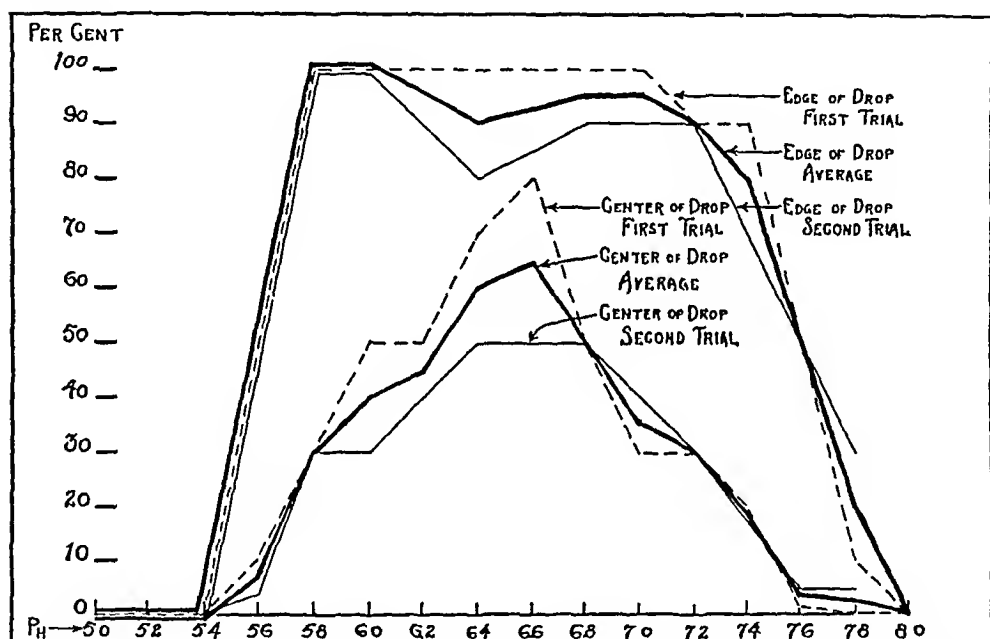


Fig 7—Completeness of sickle cell formation of the patient's corpuscles, estimated in percentage, at various hydrogen ion concentrations. Ethylene was used to exclude air. The determinations were made on suspensions prepared from washed corpuscles and the various buffer solutions

The fact that the patient's corpuscles assumed a sickle cell shape in alkaline suspensions up to  $p_H$  7.8, whereas the corpuscles of his symptomless relatives did not assume a sickle cell shape except in suspensions on the acid side of  $p_H$  7.4, is consistent with the greater susceptibility of the patient's corpuscles as shown by wet smear cultures. However, the patient's corpuscles were washed free from plasma, whereas those of the relatives were not. Furthermore, the physiologic sodium chloride used for the washing was later shown to have a  $p_H$  6.8. When the patient's blood was added directly to the buffer solutions, results were obtained in fair agreement with those for the relatives, as shown by curve A, figure 8.

Great numerical accuracy is not claimed for these determinations. The actual hydrogen ion concentration of the liquid phase of the altered

suspensions was not measured. Dilution of the buffer solutions as well as the addition of blood proteins and salts must have changed the hydrogen ion concentration from its previously measured value. The stream of ethylene also doubtless altered the hydrogen ion concentration by sweeping out of the gas chamber all traces of carbon dioxide, thus causing a shift in the whole train of equilibria among gaseous carbon dioxide, dissolved carbon dioxide, carbonic acid and sodium bicarbonate.

However, this series of determinations proves that acidification up to the point of beginning hemolysis, favors the sickle reaction. Since an increase in hydrogen ion concentration favors the dissociation of

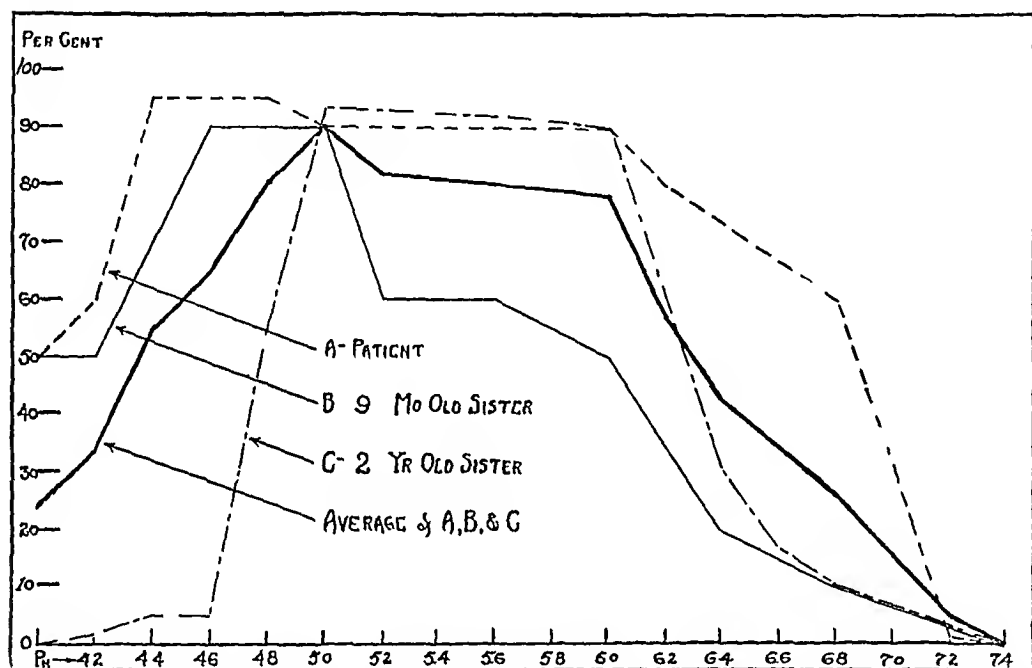


Fig 8—Completeness of sickle cell formation of susceptible corpuscles, estimated in percentage, at various hydrogen ion concentrations. Ethylene was used to exclude air. The corpuscles were not washed. Curves B and C represent averages of (1) determinations on drops prepared by mixing corpuscle suspension with buffer solution on cover slips, and (2) determinations on suspensions prepared by adding citrated blood to buffer solution. Curve A represents the averages of two series of determinations on drops prepared as designated above by (1).

oxyhemoglobin, the effect of hydrogen ion concentration on the sickle reaction is precisely what would be predicted from our hypothesis relating the distortion to the state of the hemoglobin within the corpuscles.

#### SHIFT OF HYDROGEN ION CONCENTRATION ALONE DOES NOT CAUSE SICKLE CELL FORMATION

In the course of the experiments just reported, the effect of acid and alkaline solutions on the corpuscles prior to the displacement of air from

the gas chamber was observed many times, and in no instance did sickle cell formation occur

As a further control, small drops of the suspension of the patient's corpuscles were mixed with large drops of buffer solutions of  $p_H$  varying by 0.2 from  $p_H$  4.4 to  $p_H$  8. After thorough mixing of the drops, cover slips were applied and sealed with petrolatum. The preparations were examined at intervals for two hours. No sickle cells appeared in any of the smears.

#### SICKLE CELL FORMATION INDEPENDENT OF OSMOTIC PRESSURE

It became necessary to investigate the effect of osmotic pressure on the sickle cell formation phenomenon because the buffer solutions, prepared by the method of Clark and Lubs<sup>22</sup> differed in concentration of salt.

Three series of experiments were performed. In each, the patient's washed corpuscles were added to the specially prepared solutions and then tested for the sickle reaction with ethylene.

In the first series, the hydrogen ion concentration of 0.9 per cent sodium chloride solution was altered by adding traces of acetic acid and sodium hydroxide to make a series corresponding to the buffer solutions. Sickle cell formation occurred over a range of hydrogen ion concentrations roughly comparable to those found adequate when buffers were employed.

In the second, enormous changes were made in the osmotic pressure of a buffer solution of  $p_H$  5.6 by diluting it with freshly distilled water and by adding 10 per cent sodium chloride solution. The solutions thus prepared formed a series of practically constant  $p_H$  and of sodium chloride concentrations varying from 0.2 per cent to 2.2 per cent by 0.2 per cent intervals. Sickle cell formation occurred in every case from the point of beginning hemolysis in the more dilute solutions up to extreme crenation in the more concentrated.

In the third, solutions of sodium chloride were prepared varying in concentration from 0.5 per cent to 1.2 per cent by intervals of 0.05 per cent. Each solution was tested colorimetrically before use, and the hydrogen ion concentrations were all found to lie between  $p_H$  7.2 and  $p_H$  7.4. Sickle cell formation occurred in all the dilutions with the exception of those causing hemolysis.

These results indicate that osmotic pressure has no influence on the sickle cell formation phenomenon between the points of beginning hemolysis and extreme crenation. The failure of corpuscles which have lost their hemoglobin to undergo sickle cell formation is consistent with our hypothesis relating the distortion to the hemoglobin.

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<sup>22</sup> Clark and Lubs, referred to by Clark, W. M. *The Determination of Hydrogen Ions*. Baltimore, Williams & Wilkins Company, 1920 p. 75.

## SICKLE SHAPE DISTORTION OF A CORPUSCLE

The first change noted in a corpuscle eventually forming a perfect sickle is a subtle change in the refractility of the erythroplasm. Next, a blotchy opacity appears at one side in the very rim of the biconcave disk and extends across the disk in radiating lines. This parietal opaque focus grows thicker, and the opposite side of the disk becomes thinner until it is scarcely visible. Meanwhile, the side on which the opacity first appeared decreases its curvature, and the thinned out opposite side is stretched from horn to horn of the resulting half moon. As the change progresses, the horns become longer, and the attenuated side becomes concave, until a slender crescent is formed. Generally, before this end stage is reached, several sharp processes are extruded from the convex side, producing a crisp brushlike appearance.

When oxygen is admitted to the sickle cell, the resumption of the circular form is startling in its abruptness. The sharp processes are retracted, the concave border swells out, the curvature of the convex border increases, and the mottled opacity is replaced by the normal degree of transparency.

THEORY OF THE PATHOGENESIS OF THE HEMOLYTIC ANEMIA  
OF PERSONS WHOSE BLOOD CONTAINS SICKLE CELLS

It is impossible for us to conceive of the sickle cell trait as a disease in the ordinary sense. It is hereditary and is compatible with good health and long life. However, it predisposes those affected by it to hemolytic anemia. It is possible that the mechanism of sickle cell formation *in vitro*, established by our experiments, may be related to the pathogenesis of this anemia.

It is reasonable to suppose that sickle cells are formed in the body of an affected person wherever the oxygen tension and hydrogen ion concentration are such as to render the distorted form of the corpuscles stable. It is also probable that a condition of general anoxemia would induce the formation of sickle cells *in vivo*.

If corpuscles are permanently damaged by the sickle distortion or are rendered more susceptible to hemolytic influences while distorted, anemia would be the inevitable result of anoxemia.<sup>23</sup> Vigorous phagocytosis of sickle cells *in vitro* has been observed by Sydenstricker, and large mononuclears with phagocytosed corpuscles have been observed repeatedly in stained smears of the circulating blood of patients with sickle cell anemia.

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<sup>23</sup> Cooley, T. B., and Lee, Pearl. The Sickle Cell Phenomenon, *Am J Dis Child* **32**: 334 (Sept.) 1926. The authors report that sickle cells undergo hemolysis quickly at incubator temperature whereas normally shaped cells of the same subject do not.

Anoxemia, then might constitute at least one of the unknown factors hypothecated by Sydenstricker<sup>8</sup> and Graham<sup>9</sup> which make the difference between latent sickle cell anemia and active sickle cell anemia. According to this view, if the sickle cell trait were universal, pulmonary and cardiac disease reducing oxygen tension in the body invariably would be attended by anemia and jaundice.

It is admitted that this theory rests in part on assumptions. However, there is considerable evidence in the reported case histories to support it. Table 4, summarizing the essential data of the thirteen cases reported in detail, shows that evidence of pulmonary pathologic change occurred in 60 per cent of the patients and evidence of cardiac pathologic change in 100 per cent. In one of Huck's cases and in our case a preliminary diagnosis of mitral insufficiency was made. Huck's other

TABLE 4—*Summary of Essential Clinical and Laboratory Data from Reported Patients with Active Sickle Cell Anemia\**

Case	Green Sclera	Joint Pain	Ulcer of Leg	Abdominal Pain	Liver Enlarged	Spleen Enlarged	Pathologic Change of Lung	Heart Enlarged	Heart Murmur	Improved by Rest	Albuminuria	Cast	Bile in Urine	Van den Bergh Test Direct	Van den Bergh Test Indirect and Units of Serum Bilirubin	Increased Urine Urobilin	Limits of Hemolysis Sodium Chloride Concentration, Percentage	Reticulocytes Percentage of Red Cells
Herrick	1	+	+	+	+	+	+	+	+	+	+	+	+					
Washburn	2	+	+	+	+	+	+	+	+	+	+	+	+					
Cook and Myer	3	+	+	+	+	+	+	+	+	+	+	+	+					
Mason	4	+	+	+	+	+	+	+	+	+	+	+	+					
Sydenstricker et al	5	+	+	+	+	+	+	+	+	+	+	+	+				0.53-0.25	
Sydenstricker et al	6	+	+	+	+	+	+	+	+	+	+	+	+				0.30-0.18	25
Huck	7	+	+	+	+	+	+	+	+	+	+	+	+	4	4	+	0.45-0.26	24
Huck	8	+	+	+	+	+	+	+	+	+	+	+	+			+	0.45-0.24	24
Graham	9	+	+	+	+	+	+	+	+	+	+	+	+			+		30
Moser and Shaw	10	+	+	+	+	+	+	+	+	+	+	+	+			+	0.34-0.16	30
Anderson	11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0.28-0.20	
Hamilton	12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0.35-0.20	6
Browne	13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0.42-0.23	9
Hahn and Bierman	14	+	+	+	+	+	+	+	+	+	+	+	+	+	100	+	0.32-0.22	
															29	+	0.32-0.20	19

\* Case 14 is presented in this article. The report of two cases by Cooley and Lee, footnote 23, appeared too recently for inclusion in this table. The sign + means that the phenomenon designated in the column heading was present, —, that it was absent, ±, that its presence was doubtful, a blank ( ) space, that it was not reported by the author, †, that death resulted. The figures for serum bilirubin as reported in the literature were reduced to "units," as defined by Ravdin. An Estimation of the Clinical Value of the van den Bergh Test, *Am J M Sc* 169: 850 (June) 1925, for convenience of comparison.

patient died of pulmonary tuberculosis. It is not more hazardous to assume that the instances of cardiac hypertrophy and loud systolic murmurs transmitted to the axilla were caused by primary cardiac pathologic change than it is to assume that they were altogether secondary to the anemia. It is noteworthy that several of the patients in the cases reported were greatly improved by rest in bed together with drug therapy which can hardly be supposed to have had any specific influence on the course of the disease.

The spleen cannot be left out of account in an explanation of sickle cell hemolytic anemia. Our experience indicates that the spleen plays an important part in the mechanism of the excessive blood destruction. After splenectomy was performed, startling reduction of the previously excessive rate of hemolysis was demonstrated by the chemical studies on the blood and excreta, by the hematologic studies and by the clinical improvement.

To account for this result we are not inclined to invoke the questionable hypothesis of "hypersplenism." The pathologic changes in the spleen and the changes reported by Sydenstricker suggest that the organ is more injured than hypertrophied. It is enough to assume that the spleen merely performs its usual function in sickle cell anemia, that of capturing and destroying damaged or abnormal red blood corpuscles, and that in performing this office, it is damaged itself. Splenectomy, then, is beneficial because it frees the patient from a hemoclastic organ which is, under the circumstances, too discriminating. Sickle cell anemia may be a state in which damaged or sickle shaped red blood corpuscles are preferable to none at all.

One fact in our case demonstrates that the influence of the spleen is not the cause of sickle cell formation nor of the fundamental abnormality of the erythropoietic tissue. Our patient still shows the sickle cell trait four months after splenectomy.

Sydenstricker, by inference, attributes splenomegaly in sickle cell anemia to coincident or previous malaria. Our patient presented no evidence or history of malaria, and malaria is uncommon in Indianapolis, yet his spleen was exceedingly large. It is likely that the size of the spleen in patients with sickle cell anemia depends on the stage of the disease. Although the spleen plays an active, but probably secondary, rôle in corpuscle destruction, it is, nevertheless, greatly injured by its long continued over-use, and completes its life history as an atrophic remnant of a once enlarged organ.

As regards the cause of "active sickle cell anemia," the specific characteristics of the condition are sufficiently explained by the underlying predisposition which is unique in pathology. It is unnecessary to assume an additional specific etiologic agent. Indeed, all the known facts of the disease, the geographic distribution, the restriction to negroes, the sporadic incidence of the active disease among large groups of susceptible but unaffected persons, the relatively small number of patients with active anemia in contrast with the large number of susceptible persons, makes such an assumption extremely hazardous.

In our view, it is highly desirable to distinguish sharply between the hereditary predisposition to form sickle cells and the disease which depends on it. The term "latent sickle cell anemia" is unsatisfactory

as applied to clinically healthy persons who have no demonstrable anemia. Furthermore, the term is awkward. For "sickle cell" we propose "drepanocyte,"<sup>24</sup> for the inherited trait, "drepanocytemia," for the active disease, "drepanocytic anemia."

#### CONCLUSIONS

1 The red corpuscles of persons with the "sickle cell trait" are transformed into sickle cells *in vitro* as a result of asphyxia. The transformation takes place when the oxygen tension falls below a partial pressure of 45 mm. of mercury, provided the hydrogen ion concentration is within certain limits, probably always on the acid side of  $p_H$  7.4.

2 The sickle distortion is a reversible phenomenon. Oxygen and carbon monoxide induce restoration of the discoid form.

3 All of the facts relating to sickle cells are consistent with a hypothesis that the sickle form is stable when the hemoglobin is dissociated, and that the discoid form is stable when the hemoglobin is combined.

4 The influence of hydrogen ion concentration in the sickle reaction is probably related to its influence on the dissociation of oxyhemoglobin.

5 Sickle cell formation *in vivo* is probably induced or increased by anoxemia.

6 Disease of the heart and lungs probably plays an important rôle in causing excessive hemolysis when it occurs in persons with the sickle cell trait.

7 Reasons exist for believing that the only specific cause for active sickle cell anemia is the unique hereditary anomaly of the red corpuscles which predisposes to it.

8 A patient with active cell anemia is reported as having been greatly improved by splenectomy.

9 The spleen probably plays a secondary rôle in the excessive hemolysis of active sickle cell anemia and is damaged in the process, passing through stages of enlargement to ultimate atrophy.

10 The influence of the spleen is not the cause of the sickle cell trait.

11 A laboratory test for the sickle cell trait is described.

12 The terms "drepanocyte," "drepanocytemia," and "drepanocytic anemia" are proposed to replace, respectively, the terms "sickle cell," "latent sickle cell anemia" and "active sickle cell anemia."

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<sup>24</sup> The word "drepanocyte" is derived from the Greek word *δρεπάνη*, sickle.

# BASAL METABOLISM IN CHRONIC MYELOGENOUS LEUKEMIA \*

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AND

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The basal metabolism in untreated patients with leukemia is characteristically elevated. No other afebrile disease, with the exception of hyperthyroidism, exhibits such a constant increase in heat production by the body. The high level of the metabolism in hyperthyroidism appears to be associated definitely with an increased or altered secretion of the thyroid gland, but the underlying factor or factors which account for this phenomenon in the leukemias still remain a matter for speculation and investigation. Many studies have been made concerning the value of determining the basal metabolic rate in hyperthyroidism, its use as an index of the course of the disease and its relation to the diagnosis and prognosis. On the contrary, observations on the basal metabolism in the leukemias have been much less frequent, and as a large number of patients with this disease are encountered at the Collis P Huntington Memorial Hospital and at the Peter Bent Brigham Hospital, it was thought that an intensive study of the basal metabolism in this condition might be of importance.

The literature on the basal metabolism in leukemia has been reviewed by DuBois,<sup>1</sup> McCann,<sup>2</sup> Boothby and Sandiford,<sup>3</sup> and by Murphy, Means and Aub.<sup>4</sup> Early investigators reported conflicting evidence as to the rate of oxygen metabolism in patients who had leukemia. In 1911, Grafe<sup>5</sup> first demonstrated the marked increase in the basal metabolism

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\* From the Medical Clinics of the Collis P Huntington Memorial Hospital of Harvard University and of the Peter Bent Brigham Hospital.

\* This paper is no. 64 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed (in part) by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1 DuBois, E F. Basal Metabolism in Health and Disease, ed. 1, Philadelphia and New York, Lea and Febiger, 1924, p. 300.

2 McCann, W S. Colorimetry in Medicine, *Medicine* 3: 1, 1924.

3 Boothby, W M, and Sandiford, I. Basal Metabolism, *Physiol Rev* 4: 69 (Jan) 1924.

4 Murphy, J B, Means, J H, and Aub, J C. The Effect of Roentgen-Ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia, *Arch Int Med* 19: 890 (May) 1917.

5 Grafe, E. Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, *Deutsches Arch f klin Med* 102: 406, 1911, Die pathologische Physiologie des Gesamtstoff- und Kraftwechsels bei der Ernährung des Menschen, *Ergebn d Physiol* 21: 464, 1923.

in both chronic lymphatic and myelogenous leukemia. He suggested from experiments on blood *in vitro* that the rise in the basal metabolism could be explained, in part at least, by an actual increase in the oxygen consumption by the exceedingly large number of white blood cells. He attributed the additional increase, not accounted for on this basis, to the increased use of oxygen by the excessive number of white blood cells stored in the body elsewhere than in the circulating blood, and growing abnormally in the marrow and often in other tissues.<sup>5</sup> Murphy, Means, and Aub,<sup>4</sup> studied the metabolism in a man with chronic lymphatic leukemia before and after treatment with radon and the roentgen rays. They observed that the basal metabolism, which was greatly elevated before treatment, decreased only slightly with irradiation, although the white blood count decreased markedly. Gunderson,<sup>6</sup> in a study of nineteen patients who had chronic myelogenous leukemia on whom sixty-two determinations of the basal metabolism were obtained, observed that the rise in basal metabolism appeared to be associated more closely with the number of immature white blood cells than with the total number of white blood cells. Striking exceptions were noticed, however, in which there was no correlation between the basal metabolism and the white blood count or the percentage of immature cells. McAlpin and Sanger<sup>7</sup> studied the basal metabolism in seven patients with chronic lymphatic leukemia, eight patients with chronic myelogenous leukemia and one patient of "mixed type" over considerable periods of time. They concluded that the metabolism rose and fell with the white cell count, and that after irradiation with roentgen rays, the basal metabolism often fell to within normal limits, rising once more as the white blood cells again increased in number. In their opinion the rise in the metabolism often preceded the increase of white blood cells and was consequently of value as one of the indications for further treatment.

In the present study an attempt has been made to determine the relationship between the alterations in the blood cells and the level of the basal metabolism. Furthermore, the significance of the latter has been considered in relation to the diagnosis and prognosis of chronic myelogenous leukemia. Two methods were used in studying the available material. First, a statistical study was made of thirty-six patients with chronic myelogenous leukemia in all phases of the disease, in whom the basal metabolism had been determined 272<sup>8</sup> times. Three of the patients on whom five determinations were made will be considered

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6 Gunderson, A. H. The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, *Boston M. & S. J.* **185** 785 (Dec. 29) 1921.

7 McAlpin, K. R., and Sanger, B. J. Blood Counts and Basal Metabolism of Leukemias Under Roentgen-Ray Treatment, *Am. J. M. Sc.* **167** 29 (Jan.) 1924.

8 Approximately one half of the data were collected prior to this study, owing to its anticipation.

separately on account of the unusual character of the blood picture. Second, intensive studies were made on five patients with chronic myelogenous leukemia in the form of daily observations of the metabolism and blood picture.

All determinations of the basal metabolic rate were made on the Roth modification of the Collins-Benedict<sup>9</sup> apparatus, usually by the graphic method. The customary cautions were observed to insure accuracy of the determinations. The basal metabolic rate was calculated from the standards of Aub and DuBois,<sup>10</sup> using the DuBois and DuBois<sup>11</sup> formula for surface area. Differential counts of the blood cells were made on at least 200 cells.

#### A STATISTICAL STUDY MADE ON TWO HUNDRED AND SIXTY-SEVEN DETERMINATIONS OF THE BASAL METABOLIC RATE IN CHRONIC MYELOGENOUS LEUKEMIA

In practically all instances the blood examinations were made at the same time as the basal metabolism determinations. From a statistical standpoint there is a possible criticism as the levels of the basal metabolism determinations were not uniformly distributed for its entire pathologic range, a large proportion were for the lower values and a smaller number for the higher ones. This factor was unavoidable and gives a slightly erroneous picture unless this fact is considered when deductions are made from the figures. Moreover, one patient (case 1) provided 104 of the total number of determinations, a fact which, however, appeared not to influence greatly the character of the averages obtained. A few other patients likewise contributed a considerable amount of the data concerning the basal metabolism, but a majority furnished three or four determinations.

#### DEGREE OF ELEVATION OF THE BASAL METABOLIC RATE

The impression is gained from the literature that low or normal values are exceptional in chronic myelogenous leukemia, and that without treatment high values are the rule. Table 1 gives the degree of elevation of the basal metabolism in sixty-one determinations on twenty-five patients with chronic myelogenous leukemia collected from the literature in which the results were suitable for comparison with the 267 determinations on our own thirty-three patients. The highest value for the

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9 Roth, P. Modification of Apparatus and Improved Technic Adaptable to the Benedict Type of Respiration Apparatus, *Boston M & S J* **186** 457 (April 6) 1922.

10 Aub, J. C., and DuBois, E. F. The Basal Metabolism in Old Men, *Arch Int Med* **19** 823 (May) 1917.

11 DuBois, D., and DuBois, E. F. A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, *Arch Int Med* **17** 863 (June) 1916.

basal metabolic rate in chronic myelogenous leukemia recorded in the literature is plus 80<sup>6</sup>. In our series a similar value of plus 81 was found in an untreated patient. No hitherto reported estimations are lower than minus 10, although in our series there were four determinations below this figure, of these the lowest was minus 16. These low values, however, occurred in patients who had recently been treated with roentgen rays. Boothby and Sandiford<sup>3</sup> found that 27 per cent of fifteen patients with myelogenous or lymphatic leukemia had a metabolism of from minus 10 to plus 10, 7 per cent between plus 11 and plus 15, 6 per cent between plus 15 and plus 20, and 60 per cent over plus 20. Of the total number of our determination, 123 or 46.1 per cent were within normal limits of variation, 4 or 1.5 per cent

TABLE 1—*The Degree of Elevation of the Basal Metabolism in Chronic Myelogenous Leukemia*

Range of Basal Metabolism	No. Estimations Recorded in Literature*	No. Estimations, Authors' Cases
-20 to -11	0	4
-10 to -1	0	53
0 to +9	5	70
+10 to +19	12	51
+20 to +29	14	43
+30 to +39	10	13
+40 to +49	7	12
+50 to +59	9	6
+60 to +69	0	9
+70 to +79	3	5
+80 to +89	1	1
Total	61	267

\* These figures are taken from the cases collected by Murphy, Means and Aub from the literature and from the estimations made by Gunderson. In the former, Meeh's formula for surface area and the Gephart and DuBois standards for normal are used. In the latter, DuBois and DuBois formula for surface area and the Aub and DuBois standards for normal are used.

were below the normal limits of variation (minus 10), and 140 or 52.4 per cent were above the upper normal limit (plus 10). In only 46 determinations, or 17.2 per cent, was the metabolism elevated above plus 30. Untreated patients showed without exception an elevation of the basal metabolism above plus 10, and the majority of the determinations in such patients was between plus 20 and plus 30. Gunderson,<sup>6</sup> who also found a large proportion of low values, properly attributed these to recent therapeutic irradiation. The high percentage of low figures in our series of patients is doubtless due to the fact that many of the estimations were made after intensive roentgen-ray or radon treatment when the patients had been without symptoms for some weeks.

The relation of treatment to the height of the metabolism is, therefore, of importance. Table 2 shows the frequency distribution of 250 estimations of the basal metabolism in relation to the number of days since the last treatment. It is important to emphasize that after recent treatment, the metabolism falls rapidly if the slight transient rise

which occurs within the first few days following treatment is disregarded. A few patients proved to be exceptions to this statement, and they are designated in table 2 by an asterisk which indicates that they were in the terminal stages of the disease and, therefore, were not responsive to treatment. The effect of treatment on the metabolism and the duration of its beneficial effect can be deduced from table 2. As will be shown later, the immediate effect of irradiation on the basal metabolism in many instances is to produce a transitory rise usually lasting two or three days. Subsequently the metabolism usually falls, the extent of the decrease depending on the amount of treatment and on the condition of the patient. The absence of high values for a period of about ninety days following the three day period immediately subsequent to treatment indicates the decrease resulting from irradiation. The fact that

TABLE 2—*The Frequency Distribution of the Basal Metabolism in Relation to the Number of Days Since the Last Roentgen-Ray or Radon Irradiation*

No of Days Since Last Treatment	Basal Metabolic Rate (Number of Estimations)											Total
	-20 to -11	-10 to -1	0 to +9	+10 to +19	+20 to +29	+29 to +39	+40 to +49	+50 to +59	+60 to +69	+70 to +79	+80 to +89	
Untreated				6	18	1		5			1	26
1 to 3		9	22	16	18	3	7	1	4	4		84
4 to 10	2	20	27	5	1							55
11 to 30	1	21	8	3			1*					34
31 to 50				1					1*			2
51 to 70			1	1	1*	1*						4
71 to 90		1	1		2*	1*			2*			7
91 to 100		1		1	1	1*			1*			5
101 to 150	1		3	2	1	5	2					14
150 +			4	10	4		1					19
Total	4	52	66	45	41	12	11	6	8	4	1	250

\* Determinations made on patients shortly before death

after ninety days high values of the basal metabolic rate begin to reappear suggests the duration of the effect from irradiation. The beneficial result on the metabolism frequently persists much longer, especially in patients who are treated in the early stages of the disease.

Many of the estimations shown in table 2 in the three day period following treatment were within normal limits. The presence of these low figures is attributed to a summation of the effects of repeated and frequent exposures to the roentgen ray prior to the final exposure which was used to estimate the number of days since treatment. In these estimations there is no transient rise following irradiation which may be associated with the fact that the metabolism was already at a low level. The metabolism does not always fall subsequent to therapy. If such is the case, this usually indicates an active or terminal stage of the disease when the metabolism is at a high level, and the roentgen-ray exposures may have little or no effect on the metabolism or the condition

of the patient. High estimations, therefore, in patients who have been treated within ninety days and not as recently as three days, suggest a poor prognosis.

#### RELATION BETWEEN BASAL METABOLISM AND BODY TEMPERATURE

The advanced stage of chronic myelogenous leukemia is usually accompanied by fever, which in itself adds an increment to the already elevated metabolism. In 206 observations on the basal metabolism in which accurate information concerning the temperature of the patient was recorded, a buccal temperature above normal was found in twenty-one patients or in 10 per cent of the total number. Fever was usually slight when it was present, but in two patients the temperature was as high as 102 F. In all instances in which the temperature was distinctly elevated, the patients were in poor condition, and the metabolism greatly

TABLE 3—*The Relation of the Average Pulse Rate to the Degree of Elevation of the Metabolism in Myelogenous Leukemia*

Number of Estimations	Range Basal Metabolic Rate	Average Basal Metabolic Rate	Average Actual Pulse	Range of Actual Pulse	Average Basal Pulse in Percentage*	Range of Basal Pulse in Percentage
4	-20 to -11	-14	56	51 to 60	89	85 to 93
53	-10 to -1	-5	62	51 to 90	101	90 to 129
66	0 to +9	+5	64	52 to 91	105	87 to 140
49	+10 to +19	+16	68	55 to 85	109	91 to 140
38	+20 to +29	+25	70	57 to 98	115	95 to 163
13	+30 to +39	+35	79	66 to 104	120	97 to 149
11	+40 to +49	+45	84	72 to 97	129	114 to 140
6	+50 to +59	+54	90	60 to 120	138	100 to 171
7	+60 to +69	+63	95	80 to 108	142	114 to 170
4	+70 to +79	+74	102	84 to 118	150	120 to 169
1	+80 to +89	+81	94	94	134	134

\* The basal pulse rate in percentage is calculated from the actual pulse rate, by assuming a rate of 60 as 100 per cent for men and 70 as 100 per cent for women.

elevated. When fever exists, the basal metabolic rate is undoubtedly elevated to a greater height than it would be if the patient were afebrile. A correction for this factor may be accomplished by the application of DuBois' work<sup>12</sup> wherein he allots an increase of 7.2 per cent for each degree (F) of fever. Since only a small percentage of the patients under observation were febrile at the time of the metabolism determination, and since the increased body temperature when present was usually slight, this factor has been disregarded, although it is recognized that it introduces a slight error.

#### BASAL METABOLISM AND PULSE RATE

Minot and Means<sup>13</sup> have investigated the correlation between the basal pulse rate and the basal metabolism in chronic myelogenous and

12 DuBois, E. F. *Basal Metabolism in Health and Disease*, ed. 1, Philadelphia and New York, Lea and Febiger, 1924, p. 330.

13 Minot, G. R., and Means, J. H. *The Metabolism-Pulse Ratio in Exophthalmic Goiter and Leukemia*, *Arch. Int. Med.* **33**: 576 (May) 1924.

chronic lymphatic leukemia, and they have found a high degree of parallelism between the two. From their data it appears that there is an average increase in the basal pulse rate of 17 per cent for each 10 per cent rise in the basal metabolism. They note that the rise in the pulse rate in leukemia is similar to that demonstrated by Sturgis and Tompkins<sup>14</sup> for exophthalmic goiter. In our patients, who had chronic myelogenous leukemia only, there was an average increase in the basal pulse rate of about 7 per cent for every 10 per cent rise in the basal metabolism. Table 3 shows the relationship between the pulse rate a minute and the basal metabolism in 242 determinations. The increase in the average pulse rate for each 10 per cent rise in the basal metabolic rate is fairly uniform. The range of variation in the pulse rate and in the basal pulse rate is shown in separate columns. While there is

TABLE 4—*The Relation of the Basal Metabolic Rate to the Average Red Blood Cell Count in Chronic Myelogenous Leukemia*

Number of Determinations	Range of Basal Metabolism	Average Basal Metabolism	Average Red Count (Millions) per Cc	Range of Red Count (Millions) per Cc
3	-20 to -11	-14	3.88	3.70 to 4.10
45	-10 to -1	-5	4.08	3.16 to 5.37
55	0 to +9	+5	3.68	1.88 to 5.28
32	+10 to +19	+14	3.12	1.86 to 4.55
26	+20 to +29	+24	3.31	2.44 to 4.64
5	+30 to +39	+35	3.71	3.57 to 3.80
5	+40 to +49	+44	3.59	2.02 to 4.43
3	+50 to +59	+54	3.09	2.34 to 3.57
6	+60 to +69	+63	2.11	1.54 to 3.51
3	+70 to +79	+72	2.38	1.57 to 3.45
1	+80 to +89	+81	2.69	2.69

considerable variation in each patient, the low and high extremes, when plotted in the form of a curve, rise uniformly. The individual variations in patients with a similar degree of elevation of the basal metabolic rate are possibly accounted for by the numerous other factors which influence the pulse rate, such as anemia and mental excitement during the tests.

#### BASAL METABOLISM AND ANEMIA

Patients who have myelogenous leukemia frequently have anemia, although in the early stages of the disease this may be absent or slight, while in the later stages it is usually severe. From the figures shown in table 4, it appears that the severity of the anemia bears no definite relation to the degree of elevation of the basal metabolic rate. When the metabolism is greater than plus 60, however, the anemia is usually more marked than when the metabolism is lower. This observation may be explained on the basis that the basal metabolism is high in the last

14 Sturgis, C. C., and Tompkins, E. The Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch Int Med* 26:467 (Oct.) 1920.

stages of the disease when the anemia is an associated condition but has no causal relationship to the high metabolism. The lack of uniformity between the basal metabolic rate and the number of red blood cells precludes the possibility that changes in the number of the red blood cells play any important rôle in elevating the basal metabolism.

#### RELATION OF BASAL METABOLISM TO WHITE CELL COUNT AND IMMATURITY OF WHITE BLOOD CELLS

Previous investigators have emphasized the relationship between the number of white blood cells in the peripheral blood and their degree of immaturity to the level of the basal metabolism in chronic myelogenous leukemia. Our own observations are presented in tables 5, 6, 7 and 8.

While it is difficult to draw accurate conclusions from general averages, it appears from the figures presented in table 5 that there is

TABLE 5—*The Average White Blood Cell Count in Relation to the Basal Metabolism in Chronic Myelogenous Leukemia*

Number of Estimations	Range of Basal Metabolic Rate	Average Basal Metabolic Rate	Average White Count (Thousands) per Cc	Range of White Count (Thousands) per Cc
3	-20 to -11	-14	133	122 to 149
48	-10 to -1	-5	353	79 to 183.6
63	0 to +9	+5	722	92 to 220.5
38	+10 to +19	+15	1181	68 to 360.0
34	+20 to +29	+24	1890	24.2 to 385.0
8	+30 to +39	+35	2201	180 to 704.0
7	+40 to +49	+45	1114	130 to 215.0
4	+50 to +59	+54	2908	213.2 to 342.4
5	+60 to +69	+63	1422	12.2 to 336.8
3	+70 to +79	+72	1298	43.4 to 241.0
1	+80 to +89	+81	3420	342.0

a gradual increase in the average white cell count as the metabolism rises until the basal metabolic rate reaches plus 40. Above this point the average numbers of white cells for each ten point increase in the basal metabolic rate is irregular and shows no constant tendency to increase. It seems possible, therefore, that there may be other factors of importance which influence the rate of oxygen consumption.

A consideration of the numerical level of the white blood cell count and the basal metabolism shows, as Gunderson<sup>6</sup> has observed, that there is not always a close correlation between the two. As shown in table 5, for each 10 per cent range of the basal metabolism either extremely low or greatly elevated white counts may be encountered, although usually high counts occurred with a high metabolism and low counts with a low metabolism.

In table 6 the percentage of the immature cells is compared with the basal metabolic rate. All white blood cells of the myelocyte series were considered to be immature. As a rule, a high basal metabolic rate appears to be associated with the occurrence of a high percentage of

immature cells in the blood stream This is not, however, an invariable observation, as a study of the variation of the percentage of immature cells within each 10 per cent range in the basal metabolic rate indicates that in some instances a high or low basal metabolic rate may be associated with either a high or a low percentage of immature cells The actual number of immature cells per cubic millimeter of blood did not show any closer correlation with the basal metabolism than the percentage number (table 7)

TABLE 6—*The Percentage of Immature Myeloid Cells in Relation to the Basal Metabolism in Chronic Myelogenous Leukemia*

Number of Estimations	Range of Basal Metabolic Rate	Average Basal Metabolic Rate	Average of Immature Cells, Percentage	Range of Immature Cells, Percentage
3	-20 to -11	-14	12.3	10.5 to 14.0
45	-10 to -1	-5	20.1	10.5 to 37.0
53	0 to +9	+5	19.1	2.0 to 32.0
33	+10 to +19	+15	21.7	6.0 to 37.0
32	+20 to +29	+24	25.1	5.0 to 43.0
7	+30 to +39	+34	25.9	3.0 to 48.5
6	+40 to +49	+45	20.6	11.0 to 29.0
3	+50 to +59	+53	33.0	29.0 to 36.0
5	+60 to +69	+63	45.0	15.0 to 67.0
3	+70 to +79	+72	41.0	30.0 to 56.0
1	+80 to +89	+81	86.0	86.0

TABLE 7—*The Number of Immature Myeloid Cells per C mm in Relation to the Basal Metabolic Rate in Chronic Myelogenous Leukemia*

Number of Estimations	Range of Basal Metabolic Rate	Average Basal Metabolic Rate	Average Number of Immature Cells (Thousands) per C mm	Range of Immature Cells (Thousands) per C mm
3	-20 to -11	-14	1.64	1.35 to 1.79
45	-10 to -1	-5	7.67	1.24 to 37.40
54	0 to +9	+5	14.65	0.11 to 59.54
32	+10 to +19	+15	31.15	1.15 to 114.68
33	+20 to +29	+24	40.26	1.21 to 121.19
8	+30 to +39	+35	129.08	0.87 to 647.68
6	+40 to +49	+45	23.11	2.08 to 51.83
3	+50 to +59	+53	98.54	61.83 to 117.36
3	+60 to +69	+64	73.59	55.69 to 105.52
3	+70 to +79	+72	53.66	13.02 to 89.17
1	+80 to +89	+81	294.12	294.12

Table 8 shows the average percentage of myeloblasts and myelocytes for each 10 per cent range in the basal metabolic rate This table illustrates that the percentage of myelocytes showed no steady increase compared to that of the basal metabolic rate, while the average increase in the percentage of the most immature forms, the myeloblasts exhibited a rather close relationship This statement is not without exception, however, as indicated by the variation in the percentage of these immature cells within each 10 per cent range of the basal metabolic rate It has been assumed that the presence of many young cells, such as myeloblasts or atypical young forms of cells, in the peripheral blood indicates a marked overactivity of the bone marrow which is com-

parable to a rapidly growing malignant tumor. If this assumption is correct, it seems probable that at least a part of the rise in oxygen consumption by leukemic patients may be caused by an increased demand for oxygen by the overactive white blood cell forming tissues.

#### RELATION OF BASAL METABOLISM TO CONDITION OF PATIENT

Grafe<sup>5</sup> made the most important observation that the severity of the leukemic process and the degree of elevation of the basal metabolism were closely associated with each other. In a review of the clinical histories of the patients studied, this is most apparent. In each patient on whom determinations of the basal metabolic rate were made at frequent intervals during the course of his illness, there appeared to be close agreement between the intensity of the symptoms and the degree of elevation of the metabolism. Clinical improvement after irradiation

TABLE 8—*The Percentage of Myeloblasts and Myelocytes in Relation to the Basal Metabolism in Chronic Myelogenous Leukemia*

Number of Estimations	Range of Basal Metabolism	Average Basal Metabolism	Myelocytes, Percentage	Range of Myelocytes, Percentage	Myeloblasts, Percentage	Range of Myeloblasts, Percentage
3	-20 to -11	-14	12.0	10.5 to 14.5	0.3	0 to 0.5
45	-10 to -1	-5	19.4	10.0 to 35.0	0.5	0 to 3.5
53	0 to +9	+5	18.3	2.0 to 29.0	0.8	0 to 3.5
33	+10 to +19	+15	20.4	6.0 to 35.5	1.8	0 to 7.0
32	+20 to +29	+24	22.6	4.0 to 41.0	2.2	0 to 8.5
7	+30 to +39	+34	22.4	3.0 to 45.0	3.5	0 to 9.0
6	+40 to +49	+45	16.9	4.0 to 25.5	4.7	0 to 25.0
3	+50 to +59	+53	29.7	21.0 to 36.0	3.3	0 to 8.0
5	+60 to +69	+63	32.4	15.0 to 45.5	12.5	0 to 29.0
3	+70 to +79	+72	29.8	26.5 to 33.0	10.8	0 to 22.0
1	+80 to +89	+81	65.0	65.0	21.0	21.0

likewise parallels the fall in the metabolism. Patients who had not recently been irradiated, and who showed the earliest symptoms of a recurrence had a moderately elevated metabolism. Those who were severely ill had a uniformly high metabolism. Those who had few symptoms, despite an elevated white blood cell count, showed a low or slightly elevated basal metabolism. It is important to recognize that, in general, the degree of the elevation of the basal metabolism seemed far more in harmony with the clinical condition of the patient than with either the white blood cell count or the differential blood count. It is not surprising that this is true, as many of the distressing symptoms associated with myelogenous leukemia, such as dyspnea, tachycardia, increased sweating, sensation of increased body warmth, loss of weight and intolerance to heat are dependent on the increased metabolism. In this respect the clinical use of the basal metabolic rate determination in leukemia is of value in the same fashion as it is in hyperthyroidism. It gives an index of the activity of the disease which is often difficult to obtain by any other single method of study.

Three patients, who are mentioned in the foregoing, were considered separately as they showed unusually acute manifestations of the disease. All were young women in whom the disease ran a rapid and acute course. In each case there was pronounced anemia, and the white blood cells were increased only moderately. The percentage of immature myeloid cells, however, was great and most of them were myeloblasts. In one patient the basal metabolic rate was plus 32, the pulse rate 104 a minute, the red blood cell count 1,400,000 a cubic millimeter and the white blood cell count 53,600 a cubic millimeter, of which 92 per cent were atypical myeloblasts. In the second patient the basal metabolic rate was plus 39, and the pulse rate was 104 a minute. Blood counts were not made on the day on which the metabolism test was performed, but previous counts showed 97 per cent of the white cells to be immature forms. In the third patient the basal metabolic rate on three occasions was plus 60, plus 51 and plus 40, the pulse rate averaged about 104 a minute. Blood counts were obtained at the time of the last two metabolism determinations. At these times the red blood cell count was 2,000,000 and 1,400,000 a cubic millimeter, the white blood cell counts were 60,200 and 28,400 a cubic millimeter, and the differential counts showed that about 90 per cent of the white blood cells were myeloblasts, and that 1 per cent were myelocytes. In these patients the degree of elevation of the basal metabolic rate seemed to be associated more with the greater degree of immaturity than with the number of white cells in the blood.

#### INTENSIVE DAILY STUDY OF BASAL METABOLISM AND BLOOD PICTURE REPORT OF CASES

The preceding statistical study has many disadvantages. The most serious of these is that a dynamic physiologic process like the basal metabolism is difficult to understand when expressed in fixed terms, such as the averages of a group of isolated estimations. Likewise a single examination of the blood at any instant may give an inadequate picture of the preceding blood changes which may have been responsible for the level of the metabolism.

In normal persons the basal metabolic rate is fairly constant from day to day. Even in persons having hyperthyroidism and a greatly elevated basal metabolic rate, a similar constancy in the basal metabolism may be seen. In patients with myelogenous leukemia, as will be shown later, there is a tendency to a more marked daily fluctuation as the rate of oxygen consumption rises and falls irregularly, and the extent of the variation from day to day often exceeds 10 per cent of the normal metabolism. A similar daily variation in the blood picture of chronic myelogenous leukemia likewise was noted. White blood cell counts which varied as much as 150,000 a cubic millimeter from one day to the

next were observed, and a daily difference in the white blood cell count of 50,000 cells a cubic millimeter was not unusual. For example, in case 1 the white blood counts on five successive days before treatment were 233,500, 329,500, 177,000, 248,000 and 198,000, respectively, a cubic millimeter. There was also a considerable daily change in the percentage of immature myeloid cells. Moreover, it is not uncommon to observe a difference of a million cells in the red blood count from one day to the next. The fallacy of stressing the relation of the white blood cell count at any given time to the basal metabolic rate is obvious.

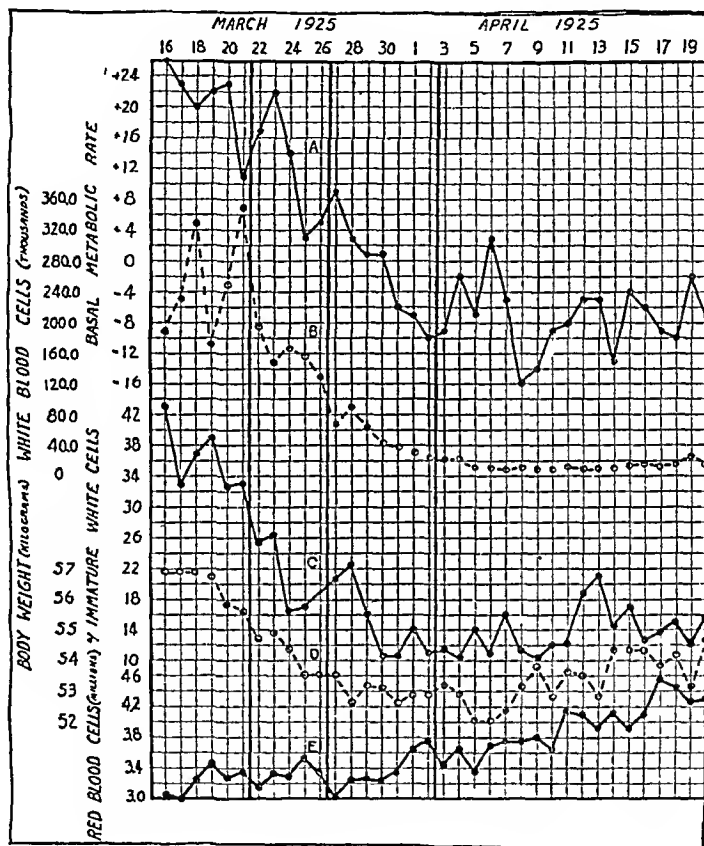


Chart 1 (case 1)—Before, during and after treatment with roentgen rays (first entry) *A*, indicates the basal metabolic rate, *B*, the number of white blood cells per cubic millimeter, *C*, the percentage of immature white cells, *D*, the body weight in kilograms, *E*, the number of red blood cells per cubic millimeter for thirty-six consecutive days in a patient with chronic myelogenous leukemia. The times of irradiation are represented by heavy vertical lines.

unless data concerning both are obtained simultaneously and at frequent intervals. Both are rapidly changing from day to day, rarely in the same direction, as may be seen by charts 1 to 7. Any isolated study of the white blood cells shows the condition of the peripheral blood at a single instant but does not give a clear indication of the labile, dynamic changes occurring in the blood stream and the blood-forming tissues which are probably associated with the fluctuation in

the basal metabolic rate. In order, therefore, to obtain more accurate information bearing on this relationship, daily observations for various periods of time were made on five patients with chronic myelogenous leukemia. These studies include observations before, during and after treatment with short wave length roentgen rays. As the following patients have been studied intensively, a brief summary of the history and physical examination of each is given below.

CASE 1—B. M., a white man, unmarried, a mechanic, aged 36, had been ill for four years. The most prominent symptoms were loss of strength and weight,

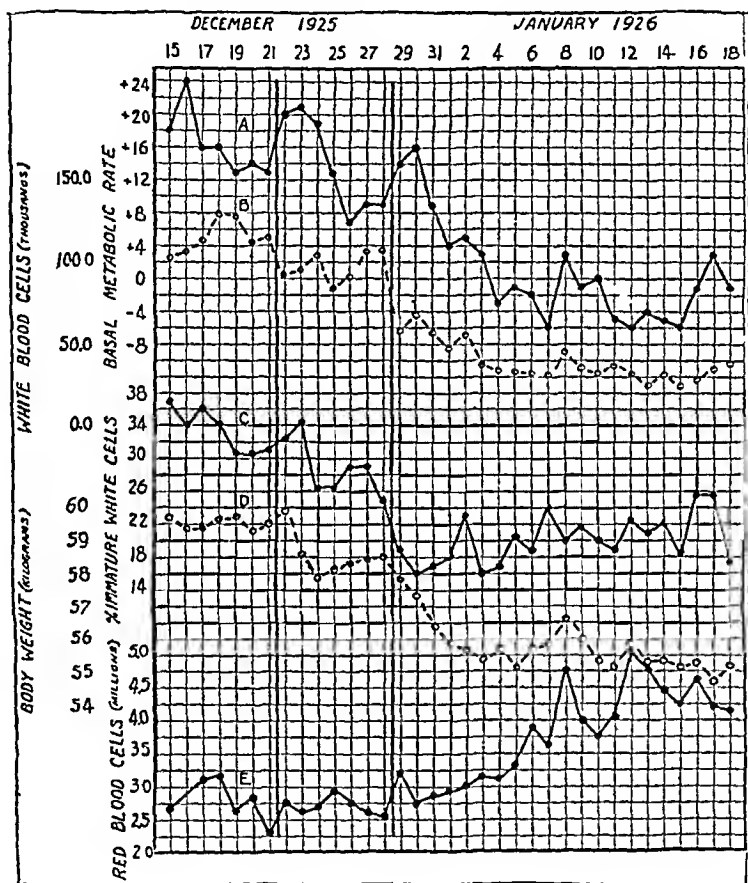


Chart 2 (case 1) —Before, during and after roentgen-ray treatment (second entry) A, indicates the basal metabolic rate, B, number of white blood cells per cubic millimeter, C, percentage of immature white blood cells, D, body weight in kilograms E, the number of red blood cells per cubic millimeter for thirty-five consecutive days in a patient with chronic myelogenous leukemia. Treatment by roentgen-ray irradiation is indicated by heavy vertical lines.

recurrent epistaxis and bleeding from hemorrhoids and vague pains in the back. The essential physical observations were pallor of the skin and mucous membranes, profuse sweating, hemorrhoids and a greatly enlarged spleen. He had received no previous treatment. He was studied on three occasions, first, beginning March 15, 1925, for thirty-six days, again for thirty-five days beginning Dec 14, 1925, and again for thirty-three days beginning March 25, 1926. During the observation periods his temperature was never elevated above normal. The observations made are presented in charts no. 1, 2 and 3.

CASE 2—B F, a white man, unmarried, an electrician, aged 49, had been ill for four years. Outstanding symptoms were weakness, dyspnea, palpitation, increased sweating, increased appetite, loss of weight and inconstant vague pain in the upper right quadrant of the abdomen. On several occasions there was hemorrhage into the gastro-intestinal tract. The important physical observations were a greatly enlarged spleen, a barely palpable liver and a hot, moist, pale skin. During the period of observation his temperature was never above normal. He had received roentgen-ray therapy five months before he came under our observation. His basal metabolic rate on previous occasions had been distinctly elevated. He was studied on two occasions, and the observations are presented in chart 4.

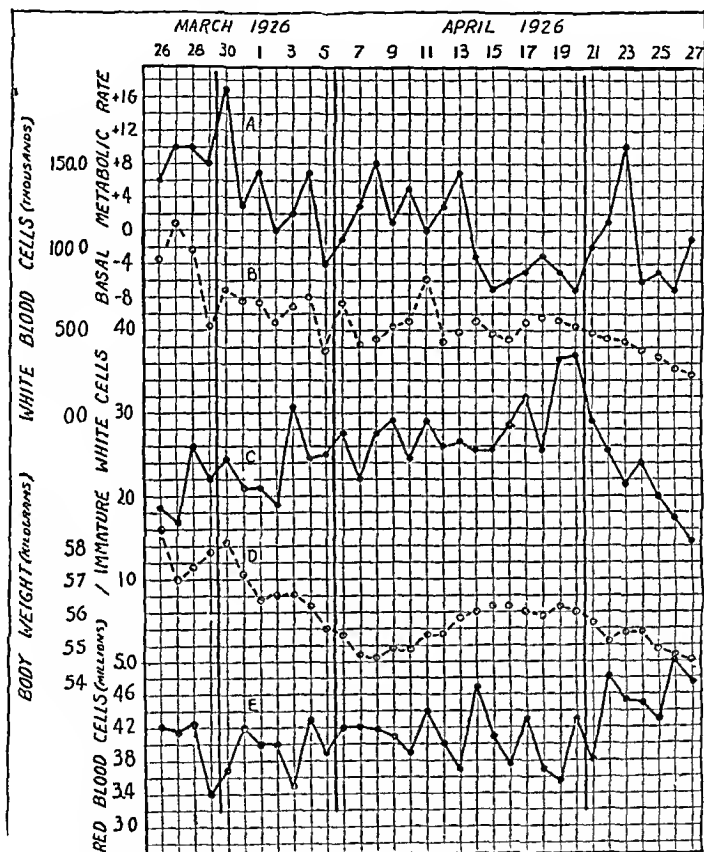


Chart 3 (case 1)—*A*, indicates the basal metabolic rate, *B*, number of white blood cells per cubic millimeter, *C*, percentage of immature white blood cells, *D*, body weight in kilograms, *E*, the number of red blood cells per cubic millimeter in a patient with chronic myelogenous leukemia (third entry) on thirty-three consecutive days, before, during and after treatment with the roentgen ray. Treatment by irradiation with the roentgen ray is indicated by heavy vertical lines.

CASE 3—H S, a mechanic, aged 35, had been ill for about eight months. The principal symptoms were weakness, diarrhea, loss of weight, intra-ocular and gastro-intestinal hemorrhage and undue bleeding following tonsillectomy at the onset of his illness. Physical observations were a moderately enlarged spleen and liver and pallor of the skin and mucous membranes. He had never been treated with roentgen rays or radon. He was afebrile during the period of observation, which lasted for fifteen days, beginning April 22, 1926. The observations on this patient are plotted in chart 5.

CASE 4—M K, a white, widowed housewife, aged 52, had been ill for three years. The important symptoms were weakness, loss of weight, dyspnea, nausea, palpitation, cough and subcutaneous hemorrhages. She exhibited marked symptoms of increased metabolism such as increased feeling of warmth, excessive perspiration and intolerance to heat. Physical examination showed a sick, emaciated woman with a pale, hot, moist skin, an enlarged heart, spleen and liver. She had an elevated body temperature rising as high as 102 F at intervals during the period of observation, which lasted for six days. Necropsy showed the observations characteristic of myelogenous leukemia. Prior to this period of observation she had received numerous treatments with the roentgen rays, the last treatment having been given about two months before death. The observations made on this patient are given in chart 6

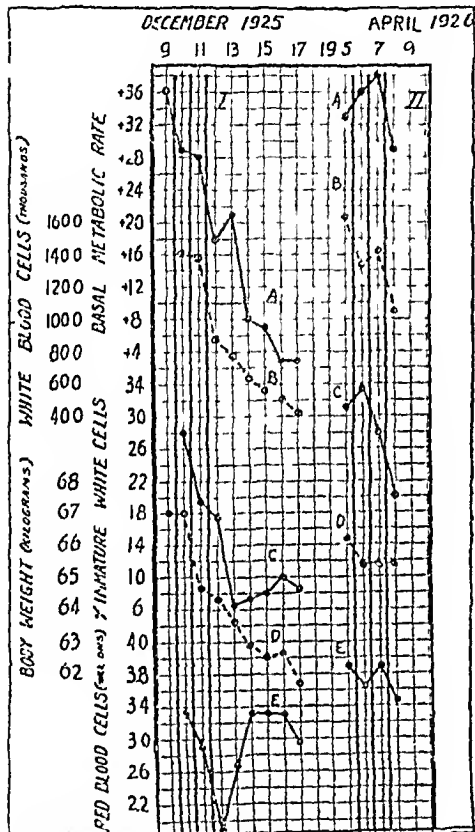


Chart 4

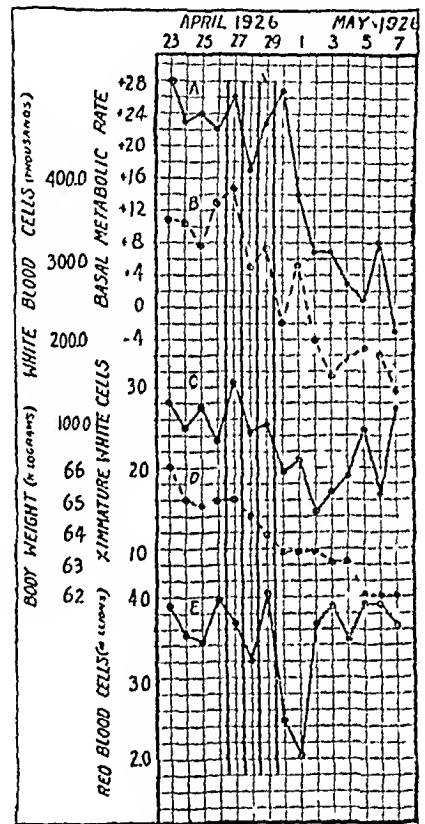


Chart 5

Chart 4 (case 2)—*A*, indicates the basal metabolic rate, *B*, number of white blood cells per cubic millimeter, *C*, percentage of immature white blood cells, *D*, body weight in kilograms, *E*, the number of red blood cells per cubic millimeter in a patient with chronic myelogenous leukemia. The patient was studied on two occasions (1, first entry for nine days and 2, second entry for four days). The roentgen-ray treatment is indicated by heavy vertical lines.

Chart 5 (case 3)—*A*, indicates the basal metabolic rate, *B*, number of white blood cells per cubic millimeter, *C*, percentage of immature white blood cells, *D*, body weight, *E*, the number of red blood cells per cubic millimeter in a patient with chronic myelogenous leukemia on fifteen consecutive days before, during and after treatment with roentgen rays. Treatment by irradiation is indicated by the heavy vertical lines.

CASE 5—M M, a white housewife, aged 47, had been ill for two years. The most important symptoms were loss of weight and strength, diarrhea, excessive body warmth and increased tolerance to cold weather. The essential physical

observations were a pale, hot, dry skin, slightly enlarged heart and greatly enlarged spleen. She had been treated previously with the roentgen ray, the last treatment having been given five months before this admission. She had an elevated body temperature throughout the period of observation which lasted for four days and terminated with death. Observations on this patient are given in chart 7.

The first patient was studied on three occasions. The periods lasted for thirty-six, thirty-five and thirty-three days, respectively. The second patient was studied on two occasions, once for nine days and again for four days. The third patient was studied on one occasion for fifteen days. The fourth and fifth patients, both in the terminal stages of the disease, were each studied for six and four days, respectively. In the two latter cases death terminated the observations. In these studies daily observations were made on the basal metabolic rate, red

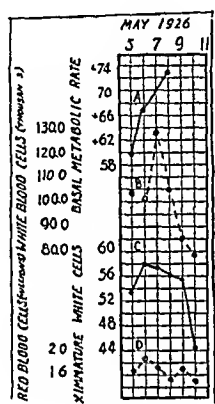


Chart 6

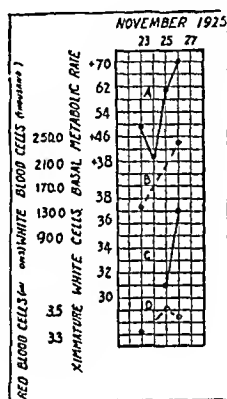


Chart 7

Chart 6 (case 5) —*A*, indicates the basal metabolic rate, *B*, the number of white blood cells per cubic millimeter, *C*, the percentage of immature white blood cells, *D*, the number of red blood cells per cubic millimeter in a patient with chronic myelogenous leukemia in the terminal stages. The patient died after six days of observation.

Chart 7 (case 4) —*A*, indicates the basal metabolic rate, *B*, the number of white blood cells per cubic millimeter, *C*, the percentage of immature white blood cells, *D*, the number of red blood cells per cubic millimeter in a patient with chronic myelogenous leukemia in the terminal stages. The patient died after four days of observation.

cell count, white cell count and hemoglobin content of the blood. Each day a differential white blood count was made on at least 200 cells. All observations were made under similar basal conditions and with standardized instruments.

Certain interesting facts, recorded below, may be observed from the charts (1 to 5). It is apparent that while the total white blood cell count and the percentage of immature myeloid cells rise and fall in a general way with the basal metabolic rate, the minor fluctuations of the basal metabolism from day to day do not correspond to the variations

in the white cell count. The red blood cell count and the percentage of hemoglobin in the blood appear to rise as the metabolism falls.

When roentgen-ray treatments are given at intervals of time sufficiently long to determine the effect of each dose, as in one patient (case 1, charts 1, 2 and 3), each exposure appears to have had a definite effect both on the cellular composition of the blood and on the basal metabolic rate. The basal metabolism after each irradiation showed an abrupt and temporary rise, lasting from one to three days, after which it fell, usually to a level lower than that before treatment. Following this transient rise there was an interval when the metabolism remained about stationary, after which it again decreased. It is significant that the initial transitory rise in the basal metabolic rate was accompanied by a fall in the total white blood cell count and in the percentage of immature white blood cells. It is also observed, on close scrutiny of charts 1, 2 and 3, that the fluctuations from day to day in the total white and differential cell count on the one hand and in the basal metabolic rate on the other appear in most cases to vary in opposite directions. As the white cell count and the percentage of immature white cells increased, the basal metabolic rate decreased, and as the former decreased, the latter increased. If a longer period of time is considered, such as a week or ten days, it will be seen that there is a general tendency of the curves of these factors to parallel each other. The failure of the number of white blood cells or the percentage of immature ones to parallel constantly the basal metabolism has been referred to before. It suggests that another factor or other factors play a rôle in producing the increased metabolism. The most logical cause to be considered is the one originally suggested by Grafe,<sup>5</sup> who thought that an overactivity of the myeloid tissues may increase the metabolism without evidence of this being clearly shown by the peripheral blood picture, as occurs in aleukemic phases of different kinds of leukemia. Therefore, one might attribute logically an increased metabolism to an overactivity of the blood-forming tissues, which for some unknown reason does not cause a true leukemic picture in the peripheral blood. Another partial cause of the elevated metabolism may be an abnormal increase in destruction of the white blood cells, which is discussed below.

In cases 2 and 3 (charts 4 and 5) the observations were somewhat different from those in case 1 (charts 1, 2 and 3). The former were treated with short wave length roentgen-ray exposures, which were given daily for from four to six days, while the latter were given single treatments at intervals of at least several days. In the more intensive method of treatment the effects of several exposures were superimposed one on the other and, therefore, the character of the change in the basal metabolic rate and the cellular composition of the

blood is different. The typical transitory rise in the basal metabolic rate following treatment in these patients is absent. Instead, it decreased, remained stationary or increased slightly during the several days of treatment. Following the course of treatment there was a fall in the metabolism, the white blood cell count and the percentage of immature white cells.

The results in case 4 (chart 6) and case 5 (chart 7) illustrate the relationship between the basal metabolic rate and the blood observations in the terminal stages of the disease. Fever, which was present in both patients, slightly modifies the results. The metabolism rose rapidly in both patients as death approached. This rise was not accompanied in case 4 by an increase in the number of white blood cells or in the percentage of immature white cells, although the latter were numerous. In this patient there was an actual decrease in the number of white blood cells as death approached. More data could not be obtained concerning these two patients on account of their serious condition. The observations in both patients indicate that the basal metabolism was a more accurate index of their condition than any other single criterion. In case 5 the patient appeared to be in a fair condition, and there was no unusual elevation of the number of white blood cells or the percentage of immature cells. The basal metabolism was high (plus 49) on the initial determination and reached plus 70 three days later. The observations were terminated by the patient's rather unexpected death. In case 4, the patient likewise had a high rate of metabolism and a relatively low white blood cell count. She died after an observation period of six days. In addition to the high rate of metabolism the seriousness of her condition was indicated by her appearance and by the high percentage of immature cells. These studies, during the terminal stage of the disease, indicate as Means and Lennox<sup>15</sup> have emphasized, that a persistently high rate of basal metabolism in patients with myelogenous leukemia suggests a poor prognosis, although the observations on the blood may not in themselves be extremely unusual. From our experience it also appears to be true that patients who have a low basal metabolic rate, in association with a high white cell count, are probably in much better condition than the blood count indicates. This point is illustrated by patients (cases 1 and 3) who had a high white blood cell count with a large percentage of immature cells in association with a moderate elevation of the basal metabolism. They were not so seriously ill as the blood picture alone would suggest, and the response to treatment in both patients was prompt.

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15 Means, J. H., and Lennox, W. G. A Study of the Basal and Nitrogenous Metabolism in a Case of Acute Leukemia During Roentgen-Ray Treatment, *Arch Int Med* **32** 705 (Nov.) 1923.

## COMMENT

The underlying causes of the increased basal metabolism in chronic myelogenous leukemia are not entirely clear. The commonly accepted theory is the one originally advanced by Grafe,<sup>5</sup> in which he suggests that the elevated metabolism is due to three causes: (1) an increased consumption of oxygen by the leukemic blood, (2) the use of oxygen by the leukemic cells elsewhere in the body than in the peripheral blood, (3) the increased demand for oxygen by the overactive tissues which are responsible for the production of the large numbers of white blood cells. It seems a reasonable deduction to conclude that the first factor is of some importance, and it is supported by the experiments of Grafe<sup>5</sup> on leukemic blood *in vitro*. This investigator calculates, however, that in patients with lymphatic leukemia in whom there is a tremendous increase in lymphocytes, the circulating blood accounts for only about 10 per cent of the total oxygen consumption by the patient. Moreover, in patients with a total white blood cell count in the vicinity of 200,000 per cubic millimeter, the elevation of the oxygen consumption by the blood alone is trivial, as he estimates that it accounts for only 3 per cent of the total amount of oxygen which is consumed. The use of oxygen by white blood cells stored in various tissues of the body and by the overactive hematopoietic tissues are factors which are difficult to evaluate. It appears reasonable to suppose that they do play a rôle in the elevation of the metabolism, but it is impossible to estimate accurately their importance.

As it does not seem that the suggestions of Grafe,<sup>5</sup> are adequate in accounting for the entire increase in metabolism, we have considered other factors that might be important. The only additional one that seems worthy to evaluate is the character and the rate of destruction of the white blood cells. Very little is known about this, but it seems possible that it may have some relation to the level of metabolism. This is suggested because directly following irradiation, large numbers of white blood cells were destroyed and the rate of metabolism increased, while the total white cell count and the percentage of immature white blood cells diminished. The rise was not caused by fever, as the patients showing this phenomenon most clearly were afebrile throughout the period of observation. It is also interesting to recall that there was usually no parallelism between the minor fluctuations of the basal metabolism from day to day and the total white cell count or the percentage of immature white cells. On the contrary, there was more of a tendency to an inverse relationship. The possibility of a relationship between the metabolism and destruction of the white blood cells is offered as a suggestion, which has not been proved. It is probable that other unknown factors likewise are of importance in this connection.

## SUMMARY

1 The basal metabolic rate in untreated patients with myelogenous leukemia is elevated with few exceptions above the normal limits, although in some instances the increase is slight. In general, the degree of elevation depends on the severity of the leukemic process and is of value in indicating the prognosis.

2 Irradiation of the patients with roentgen rays usually produces a transitory rise in the basal metabolic rate for not more than three days. In patients who are benefited by treatment this rise is followed by a rapid fall to normal limits, where it usually remains for from three to six months and in some instances even longer. Patients in the terminal stages of the disease, however, continue to have an elevated metabolism despite treatment.

3 There is a direct correlation between the pulse rate and the degree of elevation of the metabolism.

4 There appears to be no fixed relationship between the basal metabolic rate and the degree of anemia.

5 The basal metabolism is frequently high with high white blood counts and low with low white blood counts.

6 The basal metabolism is usually high when the percentage of the young myeloid cells is great, and especially when their degree of immaturity is marked.

7 Intensive daily studies showed that there appeared to be an inverse relationship between the minor fluctuations of the basal metabolic rate from day to day, on one hand, and fluctuations of the number of white blood cells and the percentage of immature forms, on the other hand. The general level of the basal metabolic rate, however, depended on the degree of elevation of the total white blood cell count and of the percentage of immature myeloid cells.

8 In addition to the commonly assumed causes of the elevation of the metabolism in myelogenous leukemia, it is suggested that the increased rate of destruction of the white blood cells may be a factor of importance.

# BILIARY, PANCREATIC AND DUODENAL STUDIES

## I THE HYDROGEN ION CONCENTRATION OF SUCCESSIVE PORTIONS OF DUODENAL CONTENTS FOLLOWING STIMULATIONS WITH MAGNESIUM SULPHATE

LAY MARTIN, M D

BALTIMORE

Among the latest and most important observations on the hydrogen ion concentration of the human duodenum are those made by Hume, Dennis, Silverman and Irwin<sup>1</sup>. Their subject was a colored man who had suffered a gunshot wound, the cause of which was unknown, and from which a duodenal fistula resulted. Their conclusions were that, "Electrometric determination of the hydrogen ion concentration of the human duodenum made by the insertion of an electrode through a fistulous opening gave a maximum  $p_H$  8.23 and a minimum  $p_H$  5.91, while the average calculated from 182 readings was  $p_H$  7.02. No definite difference in reaction was noted in observations made after the ingestion of meals consisting of fat, carbohydrate or protein."

McClure, Montague and Campbell,<sup>2</sup> having obtained their material in a more customary manner, i. e., via a duodenal tube, secured results comparable to those of the aforementioned writers. Their material was obtained from normal men. They used a Leed-Northrup potentiometer in their estimations. The observations were made, either as the patients were fasting, after they had drunk tap water, or after various single or mixed foodstuffs had been ingested. With the exception of three of their estimations, the  $p_H$  values lie between 6 and 8.102. Of the three exceptions one of  $p_H$  3.172 was between 5.101 and 7.013, the  $p_H$  5.101 was between 8.102 and 3.172. These two low readings followed the ingestion by mouth, of edestin. However, in two other instances edestin was given and followed by a relatively high  $p_H$ , certainly comparable to those obtained after the ingestion of other foodstuffs. The other reading  $p_H$  5.961 followed the oral administration of olive oil, but was obtained before the "onset" of intestinal digestion. Their conclusions are that 1. The  $p_H$  of duodenal contents varied after the ingestion of various food substances. The duodenal contents were acid

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1 Hume, H. V., Denis, W., Silverman, D. M., and Irwin, E. L. Hydrogen Ion Concentration in the Human Duodenum, *J Biol Chem* **60** 633 (July) 1924

2 McClure, C. W., Montague, A. C., and Campbell, L. L. The  $p_H$  and Buffer Values of Duodenal Contents Derived from Normal Men, *Arch Int Med* **33** 525 (April) 1924

after the ingestion of proteim and mixtures of food substances, and alkaline after the ingestion of fat and carbohydrate food substances

2 No relation was found between the  $p_H$  of the duodenal contents and the stimulation of the flow of bile and pancreatic juice. The  $p_H$  obtained either while the patient was fasting or after the ingestion of tap water was always alkaline.

McClendon,<sup>3</sup> in 1915, using his own potentiometer method, ascertained that, "The adult duodenal contents are slightly alkaline. The hydrogen ion concentration is about 0.00000002." He also made this interesting statement, "The infant's duodenum is more acid than the average acidity of the stomach. Pepsin is always present and peptic digestion must take place." He also said, "The less acid samples have a greater admixture of bile. The bile is not sufficient to make the duodenal contents alkaline." As I shall show in a subsequent paper, what he is proba-

TABLE 1—*Variations of  $p_H$  After the Ingestion of Various Foods*

Meal	Food Taken	$p_H$
Breakfast	Hot cakes, toast, coffee	3.60
	Bacon, rice, coffee	3.20
	Corn flakes and cream, eggs, toast	6.98
Luncheon	Beef, potatoes, tomatoes, pie	4.60
	Pork, potatoes, eggplant, cake	5.00
Breakfast	Hot cakes, pineapple sauce, coffee	7.21
	Toast, raspberry sauce	7.40
	Ham, eggs, toast, coffee	7.54
Luncheon	Beef, potatoes, corn, ice cream	7.00
	Beef, potatoes, bread, melon, iced tea	7.62
	Potatoes, carrots, pie, cake, ice cream, milk	7.60
	Beef, onions, potatoes, pie, cake, followed by bismuth	7.51

bly dealing with here is twofold, a larger flow of bile, and more important, a lessened amount of hydrochloric acid coming through the pylorus. Later in 1920, while working with F. J. Myers,<sup>4</sup> who obligingly swallowed the tube, he found that, "The reaction of the duodenum between 3 and 4 hours after meals was usually found to fluctuate around the neutral point, but the extreme range on the acid side was greater than on the alkaline side, possibly due to the spurting of gastric contents into the duodenum." Table 1 shows the results of McClendon's experiment.

This work well agrees with that done by Long and Fenger<sup>5</sup> in 1917. Using a Rehfuß tube, they found that the  $p_H$  values varied from 2.27 to

3 McClendon. Acidity Curves in the Stomachs and Duodenums of Adults and Infants, Plotted with the aid of Improved Methods for Measuring Hydrogen Ion Concentration, *Am. J. Physiol.* **38**: 191, 1915.

4 Myers, F. J., and McClendon, J. F. Note on the Hydrogen Ion Concentration of the Human Duodenum, *J. Biol. Chem.* **41**: 187 (Feb.) 1920.

5 Long and Fenger. On the Normal Reaction of the Intestinal Tract, *J. Am. Chem. Soc.* **39**: 1278, 1917.

781 Then estimations were made after the ingestion of regular meals. On the four subjects observed, the electrometric determinations were made at varying intervals after regular meals. The position of the bulb was controlled by the roentgen ray and varied in position from just beyond the pylorus to the proximal portions of the jejunum. With the tube in any position one is liable to obtain readings on each side of neutrality, then determinations were usually on the acid side. Long and Fenger feel that the passage of gastric chyme has a great deal to do with the  $p_H$  of the duodenal secretions, but that perhaps further down one may have to depend on other agencies for the lowered  $p_H$ .

In 1922, Okada and Arai,<sup>6</sup> working in Tokyo, reported observations made on fourteen hospital patients. They used the electrometric method, and after removing the duodenal contents at variable times, from one-half to six hours after meals, they found that the  $p_H$  varied from 4.8 to 7.97. The lowest readings were obtained in a patient with *tabes dorsalis*. All the rest were well above 6. The time of removal seems to have no definite effect on the hydrogen ion concentration.

Recently I have had the opportunity to study the hydrogen ion concentration of forty-one patients. The duodenal tube was swallowed in the approved method, and its position in the duodenum was always determined by fluoroscopic examination. At times a free flow of duodenal drainage was instituted by the mere presence of the tube in place. (I am not considering the flow of regurgitant bile sometimes obtained from the stomach.) Observations were made on this at times and were found not to vary from those which my co-workers and I obtained after our routine pancreatic biliary stimulant—40 cc of 33 per cent magnesium sulphate. This solution produces a free flow of both secretions. The former is recognized by its ferment activity,<sup>7</sup> and the latter by its color. The return flow was divided into separate tubes according to the color concentrations of the bile. It usually fell into the commonly recognized A, B and C fractions. The hydrogen ion concentration of each was estimated and will be reported with other observations that may be of interest or of pertinence.

#### METHOD

The determinations were made by the colorimetric method. The standards used were those designed by Clark and Lubs<sup>8</sup> and were exactly as recorded in Clark's book.<sup>9</sup> I am certain that the standards are accurate, as many checks were made on them.

Two complete sets were made, one was preserved with triple distilled cresol and the other was autoclaved for twenty minutes at 115 C. So far as can be

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6 Okada, S., and Arai, M. Hydrogen Ion Concentration of Intestinal Contents, *J Biol Chem* **51** 135 (March) 1922.

7 To be published.

8 Clark, W. M., and Lubs. Hydrogen Electrode Potentials of Phthalate, Phosphate and Borate Buffer Mixtures, *J Biol Chem* **25** 479 (July) 1916.

9 Clark, W. M. The Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Co., 1925, p. 81.

determined, both methods act equally well, and, provided that both sets are kept in the dark, they retain their color for considerable time, certainly for a year Methyl red fades rapidly, and this set of standards must constantly be renewed

Our method of reading is shown in the diagram

The box is that ordinarily used for the comparison of color standard sets The indicator, in amounts equal to that contained in an equal volume of colored standard, is added to the thoroughly centrifugalized duodenal contents Previous to this, small portions must be tested to determine which indicator will give the best reaction

The indicators which my co-workers and I used are thymol sulphonphthalein, tetrabrom phenol sulphonphthalein, orthocarboxybenzine azod, methyl aniline, dibromothymol sulphonphthalein, orthocresol sulphonphthalein and orthocresol phthalein

For the preparation of the stock solutions 100 mg are ground in an agate mortar with the required amount of twentieth normal sodium hydroxide<sup>9</sup> When the solution is complete, it should be diluted with water to 25 cc In making up the methyl red, we dissolved 100 mg in 100 cc alcohol and diluted this to 100 cc

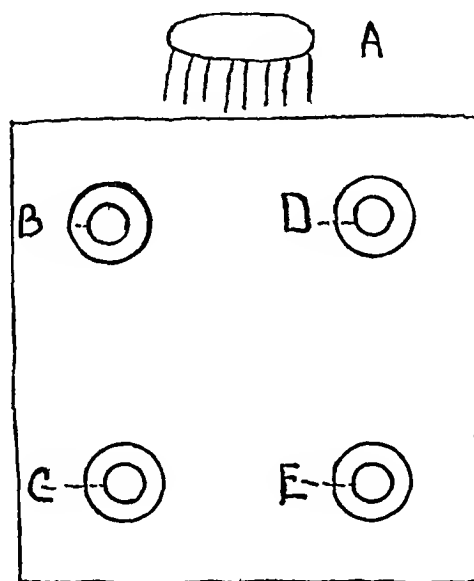


Diagram of method used in reading *A*, indicates light—substage lantern without blue glass, *B*, distilled water, *C*, unknown plus indicator, *D*, colored standard, *E*, unknown

All of our tubes were measured for us by Hynson, Westcott & Dunning, the tubes to contain the unknown substance were also of the same standard size and thickness of glass

A glance at the figures in table 2 will show how relatively rare is a  $p_H$  above neutrality In any series in which such a reading is found there is always one which is acid This has also been found in two cases of achylia In another all the readings showed acid

The only figures in the literature so far reported that can be taken as representing those to be found in the actual fasting state are those of Hume and his associates Even these are to be slightly questioned as they may be influenced by the opening of the fistula acting as a foreign stimulant

It is taken for granted that there is but little flow of bile or pancreatic juice during fasting periods. However, frequently there is a free flow of bile following the passage of a duodenal tube. Is this brought about by the action of the bulb on the walls of the duodenum, or by the gastric secretion or debris that must of course follow the passage of the tube through the pylorus?

TABLE 2—*The  $p_H$  in A, B and C Bile in Various Diseases*

Diagnosis	$p_H$ in Bile		
	A	B	C
Chronic biliary disease	5.8	5.6	4.8
Angioneurotic edema	4.4	No B	2.2
Chronic arthritis	5.4	4.4	1.2
Chronic arthritis (achylia)	8.0	5.8	8.6
Gallstones	8.4	5.6	2.8
Chronic biliary disease	4.6	6.7	1.3
Migraine	7.0	No B	1.0
Psychoneurosis	5.0	1.4	4.6
Psychoneurosis	4.6	4.6	1.3
Psychoneurosis	5.4	5.8	4.6
Psychoneurosis	5.4	2.0	5.0
Chronic biliary disease	5.8	No B	2.8
Gallstones	6.4	6.2	1.8
Gallstones	6.0	5.8	3.8
Gallstones	4.6	6.2	5.3
Chronic biliary disease	6.0	6.2	5.6
Colitis	6.8	4.6	5.8
	4.0	4.0	2.4
Banti's disease	10.0	7.0	2.4
Chronic biliary disease	8.2	6.8	6.4
Chronic biliary disease	3.8	6.4	1.4
Gallstones	6.6	4.4	3.6
Chronic biliary infection	8.8	6.9	1.8
Arthritis	6.8	7.0	6.4
Choledocholithiasis	1.6	No B	1.6
Diabetes	3.1	4.4	1.8
Arthritis	5.4	1.8	8.2
Chronic biliary disease	4.0	4.0	1.2
Chronic biliary disease	2.4	4.2	1.2
Chronic biliary disease	7.2	4.2	2.2
Chronic biliary disease	4.2	3.8	1.8
Chronic biliary disease	8.4	6.8	8.2
Migraine	4.8	4.2	3.6
Gallstones	Not done	4.7	1.9
Gumma liver	None	4.2	6.4
Chronic biliary disease	None	6.5	1.2
Gallstones	3.9	4.4	3.9
Psychoneurosis	4.6	6.2	5.3
Chronic biliary disease	6.2	6.0	6.2
Chronic biliary disease	2.4	3.9	None
Psychoneurosis	6.4	4.5	3.7

As noted before, the  $p_H$  of this unstimulated flow is comparable to the first secretion to be obtained after magnesium sulphate stimulation. This is the clear, so-called A fraction of which the  $p_H$  varies from 2.4 to 8.8, the great majority of the readings, 61 per cent, following between  $p_H$  4.2 and  $p_H$  6.8. Of forty-one determinations, only 20 per cent were alkaline. The hydrogen ion concentration in B bile is approximately the same, with a negligible quantity of alkaline. In the last portion, 61 per cent are below  $p_H$  4. Twenty-nine per cent are between  $p_H$  4 and  $p_H$  6.4. The remainder are alkaline, truly a small representation. In these fractions with such low hydrogen ion values, the presence of free and combined acids was practically always demonstrated by the use of B-amidozolethylamin and phenolphthalein.

## COMMENT

As noted before, none of the determinations made by my co-workers and myself can be accepted as representing the true fasting state of the duodenum. Our A fraction is probably the same as that which McClure, Montague and Campbell<sup>2</sup> describe as being obtained following the ingestion of food but before the beginning of intestinal digestion. This A fraction is acid in 61 per cent of the cases and usually contains pancreatic ferments, when such are to be obtained in other fractions.

If there is free acid in the stomach, the hydrogen ion concentration of the duodenum obtained through a duodenal tube after stimulations of magnesium sulphate tends in the majority of cases to become more and more acid. This can mean but one thing. Gastric acids are being projected into the duodenum. As this acidity continues, the pancreatic activity and the amount of bile pigments decrease in strength and amount. This is probably due to the fact that the stimulant acts for only a short time and not that the secretions are prohibited by the presence of acid, on the other hand, it may be a pure dilution phenomenon.

There are periods, however, when the pure biliary secretion with a rather high pancreatic activity and a high  $p_H$  will alternate with duodenal content of low  $p_H$ . Evidently the gastric secretion is coming through in spurts and the undiluted duodenal contents have a  $p_H$  bordering on neutrality or just above. From these observations, I feel that the normal duodenal contents per se are practically always nearly neutral, but that any stimulant to the gastric secretion will shortly tend to lower it.

The range of results is found to agree with those of Myer and McClendon,<sup>4</sup> Long and Fenger<sup>5</sup> and Okada and Arai.<sup>6</sup>

## CONCLUSIONS

1 After an instillation of magnesium sulphate through a tube directly into the duodenum, the resultant secretion is usually slightly acid. Usually the duodenal contents tend to become more acid the longer the tube is left there. There may be periods of neutrality or even alkalinity.

2 The normal duodenal contents are nearly neutral, but under any digestive procedure they are likely to become acid, and the lowness of the  $p_H$  is probably related to the tone of the pylorus sphincter, whether it is to be constantly acid or whether periods of acidity and neutrality will alternate.

3 Even in gastric achylia the duodenal contents are at times acid. Active pancreatic enzymes are found, however, before this chemical change is brought about. They are found in the alkaline fraction.

# THE PHYSIOLOGIC EFFECT OF MASSAGE

## SECOND CONTRIBUTION

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AND

RALPH PEMBERTON, MD

PHILADELPHIA

Increasing clinical recognition of the value of physiotherapeutic measures of various kinds makes it desirable to determine, if possible, the precise nature of the changes induced by them. Such information is important for the purpose of standardizing procedure and of ascertaining the indications and limits of practice. With the possible exception of the use of heat, massage constitutes the most valuable single form of physiotherapy. While its importance is recognized in many circles, its full value to medicine is still largely unappreciated. For these several reasons, as well as on broad grounds of physiology, a clearer understanding of its effects would have value. In a previous communication,<sup>1</sup> we pointed out that massage differs sharply in its effect from active exercise, with which it would seem to have some analogy. There is considerable evidence that its influence is chiefly, if not solely, through its effect on the circulation, but the real nature of the mechanism concerned has not been fully known.

The physiologic effect of general and abdominal massage has been the subject of considerable work in the past, though in recent years it has attracted little attention from the physiologist or biochemist. The literature up to 1910 has been reviewed by Rosenthal,<sup>2</sup> and his monograph on the scientific basis of massage contains many references to the effect of massage on metabolism. An increased urinary excretion of nitrogen following massage was observed by a number of investigators. The observation of Bendix<sup>3</sup> and also of Voigt<sup>4</sup> may be cited here, since in their experiments, in contrast to some of the earlier work, the food intake of the subjects was carefully controlled. These workers found an increased twenty-four hour nitrogen excretion on days when the sub-

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\* From the Laboratory of Clinical Chemistry Presbyterian Hospital

\* The work here reported is part of a study on arthritis in collaboration with Dr Robert B Osgood of Boston. The expense of this investigation was defrayed by contributions from several sources, including a number of patients.

1 Pemberton, R, Cajori, F A, and Crouter, C Y. J A M A 83 1761 (Nov 29) 1924

2 Rosenthal, Carl. Die Massage und ihre wissenschaftliche Begründung, Berlin, 1910

3 Bendix, B. Ztschr f klin Med 25 303, 1894

4 Voigt, Otto W. Inaug Dissert Halle, 1896

jects received massage, and Voigt also found an increased excretion of phosphorus. Following the massage, several days elapsed before the urinary nitrogen returned to the pre-massage level. Eccles<sup>5</sup> reports an increased uric acid excretion on days when massage was given. Other evidence of the effect of massage on metabolism is reported by Leber and Stuve,<sup>6</sup> who found a 10 to 15 per cent increase in oxygen consumption and carbon dioxide production, following either general or abdominal massage.

The occurrence of a diuresis following massage has been observed by a number of investigators, Hirschberg,<sup>7</sup> Bendix,<sup>8</sup> Pemberton and their co-workers.<sup>1</sup> Comparable with the excretion of nitrogen, the increase in urinary volume was found to persist for several days.

Most of the work cited in the foregoing was carried out before the advent of the more modern procedures, and in the present studies advantage has been taken of the newer quantitative methods for urinalysis to make a more detailed examination of the urine before and immediately following general and abdominal massage. It was believed that changes, directly referable to the massage, might be found in the rate of excretion of certain urinary constituents. Such changes perhaps would give further information as to the physiologic effects of massage and help to explain the undoubted benefits that result from such measures when applied to many pathologic conditions.

#### METHODS

All studies were carried out on subjects who had taken a standard breakfast from two to three hours before the collection of urine was begun. This breakfast consisted of one egg, soda crackers, butter and water. Following the breakfast, nothing further was taken until the end of the experiment. Specimens of urine covering an hour to an hour and a half were obtained before the massage, the subject resting during this time. A second specimen of urine was obtained within the half hour following a massage of from thirty-five to sixty minutes' duration, and therefore covered primarily the period of massage. The time was noted carefully, and the hourly excretion of urine calculated for the two periods.

The  $p_H$ , specific gravity and titratable acidity were measured at once. The  $p_H$  was determined colorimetrically by Felton's<sup>8</sup> spot method. For total acidity, specimens of urine were titrated to a  $p_H$  of 7.4 in the manner described by Fiske.<sup>9</sup> Folin's methods<sup>10</sup> were used for the determination of total nitrogen, chlorides and creatinine. The Folin-Benedict-Meyer method<sup>11</sup> was used for the determination of creatinine, modified so that only one-half the quantity of urine and reagents recommended by them was used. Inorganic phosphorus was determined by Brigg's<sup>12</sup> method.

5 Eccles, A. Symons. *Practice of Massage*, London, 1898.

6 Leber, H., and Stuve. *Berl klin Wchnschr* **33** 337, 1896.

7 Hirschberg, R. *Bull general de therap* **113** 241, 1887.

8 Felton, L. D. *J Biol Chem* **46** 299 (April) 1921.

9 Fiske, C. H. *J Biol Chem* **49** 163 (Nov) 1921.

10 Folin, Otto. *Laboratory Manual of Biological Chemistry*, ed 3, New York and London, 1922.

11 Benedict, F. G., and Myers, V. C. *Am J Physiol* **18** 397, 1907.

12 Briggs, A. P. *J Biol Chem* **53** 13 (July) 1922.

TABLE 1—Composition of Urine Secreted Before and During a General Massage, Following a Standard Breakfast\*

Case	Date	Volume, Cc per Hour		Specific Gravity,		pH		Titratable Acidity Cc Tenth Normal Acid per Hour		Sodium Chloride, Mg per Hour		Inorganic Phosphorus, Mg per Hour		Total Nitrogen, Mg per Hour		Creatinine, Mg per Hour		Creatine, Mg per Hour	
		Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During
1	12/15/25	37	21	1.020	1.020	6.8	5.8	4.4	5.0	240	130	12	12	279	212	51	41		
2	12/15/25	30	57	1.023	1.027	5.2	5.2	6.2	14.6	440	990	6	27	377	609	46	76		
3	12/21/25	60	60	1.007	1.007	7.0	7.0	2.6	2.1	170	240	13	10	296	329	36	33		
4	12/22/25	21	35	1.021	1.021	5.2	5.2	7.6	11.8	190	390	8	20	226	202	41	47		
5	1/21/26	15	25			5.8	5.8	2.5	4.0	28	168	4	12	35	198	33	39		
6	1/25/26	25	54	1.020	1.020	5.6	7.0	5.2	3.5	198	492	13	27	16	303	21	34		
7	1/28/26	24	44	1.020	1.021	7.4	7.6	9.7	4.6	233	396	8	18	145	247	13	23		
8	1/29/26	80	52	1.018	1.020	5.2	6.1			736	440	18	15	498	444	54	73		
9	2/ 5/26	73	99	1.016	1.014	7.6	7.2			623		15	26	398	302	45	40		
10	2/ 9/26	33	9			5.0	5.0	9.5	2.1	353	66	17	5	398	90	14	14		
11	2/11/26	16	126	1.015	1.015	5.8	6.4	11.5	7.3	1,990	1,400	25	27	572	437	60	46		
12	2/17/26	35	42	1.016	1.016	7.2	7.2	0	0	300	234	8	11	228	238	26	28		
13	2/26/26	60	92	1.011	1.010	5.6	5.4	6.9	8.2	512		15	12	315	133	50	71		
14*	3/ 2/26	40	69	1.022	1.018	6.4	7.0	4.7	1.5	474	567	10	20	351	340	41	35		
15*	3/10/26	112	229	1.010	1.007	6.2	6.6	6.7	5.8	832	727	18	23	461	494	75	66		
16*	3/31/26	19	180	1.025	1.010	6.8	6.6	0.3	6.6	179	782	7	32	304	543	26	69		
17*	4/28/26	72	74	1.019	1.020	5.2	5.6	12.5	9.4	729	706	15	13	719	746	72	76		
18*	4/28/26	57	53	1.016	1.014	5.2	5.8	7.6	7.0	337	333	9	14	470	413	42	38		
19*	4/29/26	64	249	1.020	1.011	5.8	7.3	7.4	2.1	686	1,449	17	18	753	68	99	99		
20*	4/29/26	17	31			5.4	6.2	5.7	4.2	319	558	9	6	170	320	47	69		

\* Abdominal massage included

TABLE 2—Control Experiments, Composition of Urine Following a Standard Breakfast

Case	Date	Volume, Cc per Hour		Specific Gravity,		pH		Titratable Acidity Cc Tenth Normal Acid per Hour		Sodium Chloride, Mg per Hour		Inorganic Phosphorus, Mg per Hour		Total Nitrogen, Mg per Hour		Creatinine, Mg per Hour		Creatine, Mg per Hour	
		Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During
5	1/22/26	32	75	1.023	1.020	5.8	5.6	5.5	8.2	235	271	13	20	209	232	34	31		
6	1/26/26			1.016	1.020	7.4	7.6	3.3	1.4	473	405	20	16	437	160	40	24		
7	1/27/26	65	15	1.011	1.015	7.0	6.8	4.1	2.9	430	393	15	12	331	289	22	20		
8	2/ 2/26	17	10	1.022	1.022	5.6	7.6	6.7		437	261	32	16	191	203	55	24		
9	2/ 4/26	31	11	1.022	1.025	5.8	7.6	5.3		398	218	8	12	318	407	66	59		
10	2/ 8/26	33	25			5.6	5.6	6.6	4.1	300	400	8	11	258	313	67	48		
11	2/ 9/26	74	29	1.020		5.0	5.2	11.0	8.8	502	252	18	17	335	221	37	24		
12	2/12/26	74	34			5.8	7.2	4.2	0.2	312	356	6	7	166	217	31	35		
14	2/26/26	31	107	1.021	1.016	6.4	7.2	4.6	1.7	677	939	23	24	482	482	45	46		

\* The terms "before" and "during" are used to indicate that the collections of urine were made at comparable periods and intervals, following a standard breakfast, although no massage was given.

The analytic data are expressed in terms of quantities excreted per hour for the period preceding the massage and for the period during and immediately following the massage

In table 1 are given the results of twenty experiments in which the effect of massage on the composition of the urine was studied. Abdominal massage in addition to the general massage was given in seven of the experiments (14 to 20)

The massage consisted of a vigorous general muscular massage of from thirty to sixty minutes' duration, given by a trained masseur, or masseuse. The subjects were patients who had arthritis and patients convalescing from operations. Nearly all of them were accustomed to some form of massage, therapeutically given, and consequently were suitable for receiving vigorous treatment.

In table 2 are ten control experiments performed on days when no massage was given. The specimens of urine were collected under the same dietary regimen and at the same time intervals as prevailed during the massage experiments. The subjects were the same persons who had served for the previously described experiments. The control and massage experiments were usually carried out on successive days.

### RESULTS

Examination of the tables reveals clearly that despite the standardization of the breakfast following a fourteen hour fast, and the conduction of the experiments under uniform conditions of time and procedure, the influence of the subject's previous diet was not eliminated. The wide variations exhibited in the hourly excretion of certain of the urinary constituents and the lack of uniform behavior during the pre-massage periods would seem to be ascribable, in part at least, to differences in the individual dietary habits.

These results show no marked change in the composition of the urine that can clearly be ascribed to the effect of the massage, although there are indications in some cases that the massage has had an effect on renal activity. An increase in volume of urine secreted per hour was found more frequently following massage than during the control periods. This was especially true when abdominal massage was given. Occasionally a true diuresis was observed. Increased intra-abdominal pressure accompanies abdominal massage, and this may in turn cause a diuresis. Bazett and his co-workers<sup>13</sup> have reported diuresis following the application of abdominal pressure, and they suggest that the diuresis which they observed during baths was caused by the pressure of water on the abdomen, which in turn influenced the venous blood pressure.

No effect was observed on the secretion of acid which could be ascribed to massage. This is in keeping with previous work<sup>1</sup> in which it was shown that massage produced no disturbance in the acid-base equilibrium of the blood, differing in this respect from exercise.

An increased rate of excretion of nitrogen, inorganic phosphorus and sodium chloride was found during the massage period more often

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<sup>13</sup> Bazett, H. C., Thurlow, S., Crowell, C., and Stewart, W. *Am J Physiol* 70:430 (Oct) 1924. Griffith, J. Q., and Hansell, H. R. *Am J Physiol* 74:16 (Sept) 1925.

than during the corresponding period in the control experiment. The increases in these constituents frequently are not large and do not always accompany massage.

Massage has no effect on the rate of excretion of creatinine, judging from the results of the massage and control experiments. In one case only was a definite creatinuria observed, and in this instance the rate of creatinine excretion was not changed during massage. In none of the subjects was a creatinuria induced by the massage. In our hands the method for the determination of creatine was hardly adequate to detect small quantities.

Taken as a whole, these results fail to show any marked changes of the rate of excretion of urinary constituents during vigorous muscular and abdominal massage. The benefit of massage seems, then, to depend on broad physiologic effects rather than on its influence on any specific end-products of metabolism. Rosenthal,<sup>2</sup> after reviewing the physiologic effects of massage, believes that they may be explained by an increase in the blood flow through the parts massaged. That the benefits accruing from massage probably result from changes in the circulation has also been suggested on other grounds by Pemberton, Cajori and Crouter.<sup>1</sup> The experimental results recorded in this paper further substantiate this view.

#### SUMMARY

- 1 The rate of excretion of water, acid, total nitrogen, sodium chloride, inorganic phosphorus, creatinine and creatine was ascertained in a group of subjects following a standard breakfast. The effect of vigorous muscular and abdominal massage, given under the same conditions, was also determined in respect to the rate of excretion of these urinary constituents.

- 2 An increased volume of urine frequently accompanied massage, and at times a definite diuresis was observed. This was especially true when abdominal massage was given.

- 3 Accompanying or following massage an increase was frequently, but not always, observed in the rate of excretion of total nitrogen, inorganic phosphorus and sodium chloride.

- 4 No evidence that massage influences the reaction of urine or the excretion of creatinine or creatine was obtained.

- 5 It may be concluded from these experiments that massage has no immediate or great influence on general metabolism per se. The cumulative effect which massage nevertheless exercises on various metabolic processes probably lies in its mechanical influence on the circulation of the parts concerned.

We are indebted to Mr. J. J. O'Brien, Miss Blanche Hemminger and Miss Hazel John for their willing and essential cooperation in carrying out the massage.

# THE ACOUSTICS OF THE BRONCHIAL BREATH SOUNDS

APPLICATION TO PHENOMENA OF AUSCULTATION AS  
HEARD IN LOBAR PNEUMONIA <sup>†</sup>

GEORGE FAHR, M D  
MINNEAPOLIS

It is usually taught that the typical signs of lobar pneumonia are bronchial breathing, bronchophony and increased tactile fremitus, but the onset of a lobar pneumonia is rarely associated with bronchial breath sounds, bronchophony and increased tactile fremitus, the classical signs of a lobar pneumonia as obtained by auscultation. The inspiratory breath sounds are usually vesicular in quality but much reduced in intensity or entirely absent at first. They not only are faint but also sound as if they came from a greater distance than normally. The expiratory breath sound may be fainter than the normal or slightly increased in intensity and duration. At this time not only is there no bronchophony present, but the transmission of the spoken voice may be much reduced and the tactile fremitus may be absent or reduced in intensity over the area of pneumonia. This period of faint and distant vesicular breath sounds may last only a few hours, or it may last a number of days. During the last year, I have had occasion to study carefully about forty cases of pneumonia. It was not common to find bronchial breathing, increased tactile fremitus and bronchophony present over the area of pneumonia during the first twenty-four to forty-eight hours. The majority of the patients exhibited faint and distant breath sounds of vesicular character, with decreased fremitus and transmitted voice over the area of pneumonia for from twenty-four to seventy-two hours. During this period the roentgen ray might show only a slight haziness over the area and not a dense shadow, or it might show a moderately dense shadow. When the breath sounds became distinctly bronchial, and when tactile fremitus increase and bronchophony were present, the roentgen rays always showed a dense shadow over the area of pneumonia.

The following two cases are illustrative

The patient developed a chill and stitch in the right side and pain over the abdomen, an acute appendicitis was diagnosed. Fever and leukocytosis of 30,000 were present. Forty-four hours after the onset of the pain, I was called in by the surgeon who had been asked to operate to decide concerning the presence of pneumonia. The surgeon had found the abdominal symptoms slight and could not easily reconcile an acute appendicitis with the leukocyte count of 30,000. Suspecting pneumonia, he had made a physical examination but felt that the physical signs were not convincing.

\* Read by invitation before the Lymanhurst Medical Staff, March 23 1926

† From the Department of Medicine, University of Minnesota Medical School

I found the patient exhibiting only mild dyspnea, but there was definite restriction of movement over the lower part of the thorax on the right side during respiration. Percussion revealed a high pitched, somewhat hyperresonant note over the right lower lobe. Auscultation revealed an occasional crepitant rale over this right base. The inspiratory breath sounds over the right lower lobe were faint—they seemed to come from a distance greater than normal—and the expiratory murmur was slightly, but definitely, prolonged and certainly not diminished in intensity. Tactile fremitus was absent over the right lower lobe, and the spoken voice was poorly transmitted, being less intense than on the left side. A diagnosis of lobar pneumonia involving the right lower lobe was made, and transfer to the medical service was advised. The intern assigned to the case was skeptical as to the diagnosis but the following morning, seventy-two hours after the onset, reported that bronchial breathing, increased tactile fremitus and bronchophony were present. His physical examination of the patient was confirmed, and the requested roentgen-ray examination resulted in a report of "lobar pneumonia involving the right lower lobe."

In a case recently seen, breath sounds and tactile fremitus were absent on the second day of pneumonia, at which time there was intense dullness over the whole right lower lobe and part of the left lower lobe. The physical signs suggested fluid in the chest, yet on the third day intense bronchial breathing and bronchophony were present over the dull area, and tactile fremitus was intense. This is typical of my experience with the physical signs of lobar pneumonia.

In order to understand the physical signs of pneumonia it is necessary to review our knowledge of the physics of sound and to apply it to the problems of the production and transmission of sounds in the tracheobronchial system under normal and pathologic conditions. For this purpose, sounds must be considered as sensations in consciousness brought about by vibrations of the air which is in contact with the ear drum. In the case of the normal and abnormal breath sounds and spoken voice sounds, these vibrations are produced within the tracheobronchial system and are transmitted to the thorax wall along the walls and within the walls of this system. From the thorax wall the vibrations are conducted to the observer's ear drum through the lumen of his stethoscope. The vibrations are not simple vibrations of a single frequency or pitch but are made up of a number of vibrations of different frequencies. The higher the frequency of a vibration, the higher the pitch as perceived by the observer. Physicists speak of the vibration of lowest frequency or pitch as the fundamental, and the vibrations of higher pitch as the overtones, in a sound compounded of vibrations of various frequencies. A given instrument for the production of sound will usually produce a sound made up of more than one frequency. The lowest frequency is the fundamental for that instrument and is usually much the loudest vibration produced by the instrument. As a rule, the overtones of any given instrument are less intense than the fundamental tone of the instrument.

The trachea and the bronchial tree compose a system of tubes of varying length and internal diameter connected with each other and with rigid walls down to the bronchi of about 2 mm diameter. The laws and theories of physics that relate to the production of sounds in pipes

and the transmission of sound waves through tubes must therefore be applied to the problems of the production and conduction of the bronchial breath sounds in the lungs of man, if the difference in the physical signs at the onset and later in the disease is to be understood

There are two kinds of pipes so far as the physics of sound production is concerned, namely, the reed pipe and the labial pipe. In the reed pipe, a vibrating tongue or membrane set into motion by a stream of air produces a sound the pitch of which is partly determined by the dimensions and elastic coefficient of the vibrating part and partly determined by the dimensions of the pipe. The pitch of a reed pipe is prac-



Fig 1—Schematic cross-section of labial organ pipe showing pendulating air current as demonstrated by smoke in issuing air current. In the tracheobronchial system the sharp edge at the points of bifurcation functions during inspiration as a lip in a labial pipe. (From Myers and others "The Normal Chest," to be published by Williams & Wilkins Company, Baltimore, 1926.)

tically invariable when the velocity of the air blowing the reed is increased. Air under pressure issues from a narrow opening and strikes against a sharp edge in the typical labial pipe. The issuing air column is thrown into vibration about the sharp edge (fig 1), and vibrations of this air column which are of the same pitch as the fundamental tone of the pipe or one of its overtones are reinforced in intensity by resonance with the column of air in the pipe, and a sound is secured the pitch and quality of which are determined largely by the dimensions and material of the pipe.

If one blows through a glass T tube, a sound is produced. The air issuing from the side tube at high velocity is set into vibration both as

it leaves the side tube and emerges into the other tube and as it strikes against the wall of the other tube. Vibrations whose frequency corresponds to the fundamental frequency of the tube in which the vibrations have been produced set the air in this tube vibrating at this frequency, and a sound is produced the pitch of which corresponds to the fundamental frequency or pitch of the tube into which air has been blown. The same sound is produced if the two tubes do not meet at a right angle (fig 2). Tubes such as this are to be classed with the labial pipes so far

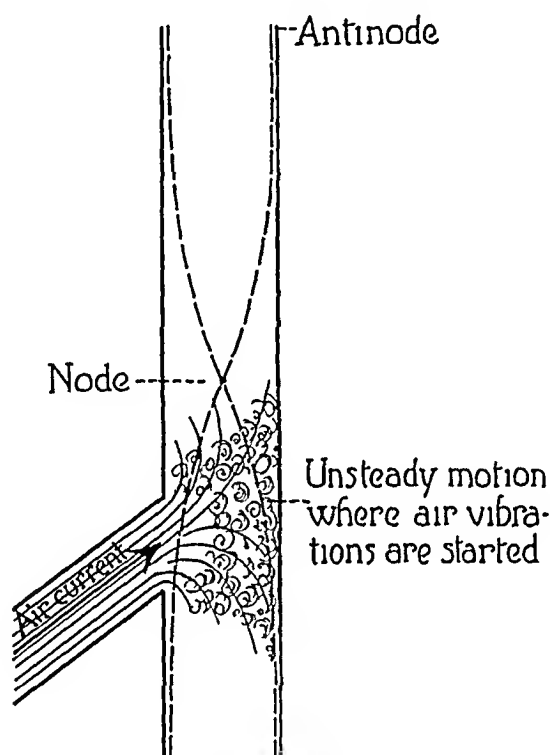


Fig 2—Schematic representation of the conditions in the tracheobronchial system during expiration. Air moving through the side branch with considerable velocity emerges into the main tube and is set into vibration as it leaves the side branch and also as it strikes on the opposite wall of the main branch. This sets up vibrations of the air in the main branch of a frequency corresponding to its fundamental pitch. At the ends of the main tube there are antinodes and in the middle nodes according to the well known law of open pipes.

as sound production is concerned, for the mechanism of the sound production is practically the same as that in the true labial organ pipe. The pitch of the sound produced by a labial pipe is not invariable as in the reed pipe, for if the velocity of the stream of air blowing the pipe is increased sufficiently, a point is reached at which the pitch of the sound produced jumps up one whole octave, if the speed of the stream of air is increased still further, a velocity is reached at which the pitch jumps another octave. The velocity of the air blown into a labial pipe can then, to a certain extent alter the pitch of the sound and this alteration is always of the nature of one or two octaves' increase in pitch.

The first problem is to determine whether the bronchial breath sounds are produced by a reed pipe or by a system of labial pipes, and then to determine where this pipe or these pipes are located in the bronchial tree. Bushnell<sup>1</sup> has maintained that the bronchial breath sounds are produced by vibrations set up in the vocal cords by the passage of air through the vocal cords, and that the intensity and character of the sound is modified by resonance in the trachea and bronchial tubes, in other words, Bushnell believes that the tracheal and bronchial breath sounds are produced by a reed pipe system. Many simple experiments show that this cannot well be the case. If a stethoscope is placed over the trachea or larynx and air is breathed in and out at normal velocity, a tracheal tone is heard which has the normal pitch of the tracheal tone. If the observer now blows air out under extreme exertion, thus increasing the velocity of the column of air, he can get the pitch to jump one octave or even two. I have had two competent musicians auscultate my own tracheal tones during normal expiration and during extremely forced expiration, and they both assured me that the pitch jumped one octave on forced expiration. On one occasion, one of the musicians heard it jump two octaves. This experiment seems to show that the tracheal tone is produced by a labial type of pipe.

Martini,<sup>2</sup> who deserves the credit for emphasizing the labial pipe character of the tracheobronchial breath sounds, has auscultated the tracheal breath sounds over the vertebra prominens after passage of a tracheoscope so that the vocal cords could play no part in the production of the sound, and he has found the tracheal tone present and little altered. I have auscultated the tracheal tones over the trachea and vertebra prominens, and the bronchovesicular breath sounds over the right apex, in a number of persons before and after the passage of the bronchoscope, and I have found only a little change in the breath sounds. Recently, I had the opportunity to auscultate a patient who had had the larynx removed surgically. He breathed through a tracheotomy tube inserted into the trachea about 2 inches (5 cm) below the point where the larynx had been cut off. The breath sounds everywhere were normal. The tracheal sounds auscultated over the vertebra prominens were normal, and could be heard with diminishing intensity down to the third dorsal spine. Their pitch was higher than that of the average normal person and the intensity was somewhat less than that of the average normal person. The bronchovesicular breath sounds in the second right interspace were bronchovesicular in character in this patient. The breath sounds over the right apex in the

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1 Bushnell and Pratt. *Physical Diagnosis of Diseases of the Chest*, Philadelphia, 1925, p. 37.

2 Martini. *Studien ueber Perkussion und Auskultation*, Habilitationsschrift, Munchen, 1922.

supraclavicular fossa closely approached bronchial breath sounds in character. These sounds were less intense and slightly higher in pitch than in the average normal person, yet on auscultating a large number of normal persons, I could find some whose breath sounds in this area resembled those heard in the patient without a larynx. A complete survey of the breath sounds in this patient over all areas resulted only in determining that the pitch of the tracheal and bronchial breath sounds was higher than in normal persons and probably less intense. The glottis, therefore, plays only a minor part in the production of the tracheal and bronchial breath sounds.

Bullar<sup>3</sup> has shown on exenterated calf lungs that the inspiratory vesicular murmur is formed in the air sacs themselves, and that the bronchial breath sounds are formed largely in the trachea and larger bronchi. In his experiments, the left lung was fitted air tight into an artificial thorax and the right lung was outside the thorax in a state of massive collapse. The two lungs were connected by the trachea, which was cut off below the larynx. A bronchial breath sound was heard over the right collapsed lung outside the thorax when inspiration was produced in the left lung by lowering the pressure outside this left lung in the artificial thorax. When a plug was inserted into the trachea, and when air was forced out of the left lung and into the right lung by increasing the pressure in the artificial thorax outside the left lung, a vesicular inspiratory murmur was heard over the right lung, in other words, when air entered the air sacs of the right lung, a vesicular inspiratory murmur was heard. These experiments prove that the glottis plays a minor part in the production of the bronchial breath sounds. It may be concluded from the foregoing experiments that the tracheobronchial breath sounds are produced by labial pipes, because vibrations of the glottis play no important part in the production of the bronchial breath sounds, and it contains the only available membranes for the production of sound within the tracheobronchial tubing.

During inspiration the mechanism of formation of the inspiratory bronchial breath sound corresponds closely to the mechanism of the organ pipe in figure 1. The air current striking on the bifurcation points of the tracheobronchial system is set into vibration at these sharp edges, and the resulting sound has the pitch of the tube in which these vibrations are present. During expiration the mechanism is largely as represented in figure 2. As air emerges from a smaller system into a larger one, it is set into unsteady motion or vibration, and these vibrations set up sound vibrations of pitch corresponding to the dimensions of the larger tube into which the air is emerging.

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3 Bullar. Experiments to Determine the Origin of the Respiratory Sounds, Proc Roy Soc London 37 441, 1884

The various tubes making up the bronchial tree are of different lengths and diameters and therefore will have different fundamental periods of free vibration or pitch. If the length of an open pipe is doubled, the pitch of the fundamental is reduced one octave. The width of a pipe has a certain influence on its pitch also in that a diminution in diameter tends to lower the pitch of the fundamental. If the walls of a pipe become less rigid, the pitch becomes lower and the sound character or timbre changes somewhat. It is therefore logical to suppose that the bronchial breath sounds contain vibrations of different frequencies, and it is of interest to know what these frequencies are and what bronchi are concerned in their production.

Martini and Mueller<sup>4</sup> have done an excellent piece of work on the production and conduction of the bronchial breath sounds. Martini<sup>4</sup> had shown by graphic methods that the bronchial breath sounds in two patients examined by him had a pitch between  $e^1$  and  $d^2$ , that is, a frequency between 320 and 540 vibrations a second. By means of resonators he determined that the bronchial breath sounds also contained overtones of approximately 1,000 vibrations a second, or around  $c^3$  on the musical scale. Cabot and Dodge<sup>5</sup> have shown by means of the stethophone that the lowest frequency of the bronchial breath sounds lies between 240 and 400 vibrations a second, and that the highest lies between 660 and 1,000 vibrations a second. Working with the original model of the stethophone in Dr. H. B. Williams' laboratory, department of physiology, Columbia University, I found the tracheal breath sounds largely composed of vibrations between 400 and 660 vibrations a second. A not inconsiderable portion of the sound energy consisted in vibrations between 660 and 1,000 a second. A small amount of the sound energy consisted of vibrations between 120 and 400 a second.

With the knowledge that the bronchial breath sounds have a fundamental of about 300 to 500 vibrations a second, and that they contain overtones of a frequency around 1,000 a second, Martini and Mueller determined to find just what parts of the tracheobronchial system of labial pipes could produce vibrations of this frequency. They first recorded graphically the vibrations set up in the system of tubes comprised of the mouth, nasal cavities and tracheobronchial system of a person connected by a glass T tube in the mouth to a recording optical capsule on the one side and closed by a condom rubber on the other side of the T tube. When the rubber membrane was burned through, a number of free vibrations of the system were produced, and these were recorded by the optical capsule on a photographic drum. The free vibra-

<sup>4</sup> Martini and Mueller. Studien Ueber das Bronchialatmen, *Deutsches Arch f. klin. Med.* **143** 159, 1923.

<sup>5</sup> Cabot and Dodge. Frequency Characteristics of Heart and Lung Sounds, *J. A. M. A.* **84** 1793 (June 13) 1925.

tions of this system were investigated in five persons. The fundamental frequency of this system recorded in this way varied between 400 and 600 vibrations a second. They then proceeded to measure the fundamental frequency of the tracheobronchial system below certain levels. In order to do this, it was necessary to make use of lungs taken from the bodies of patients who had recently died. Then the system was cut through at various levels and the T tube, with recording optical capsule on one arm and the condom membrane on the other, was inserted into the distal end of the cut bronchus. When the condom membrane was

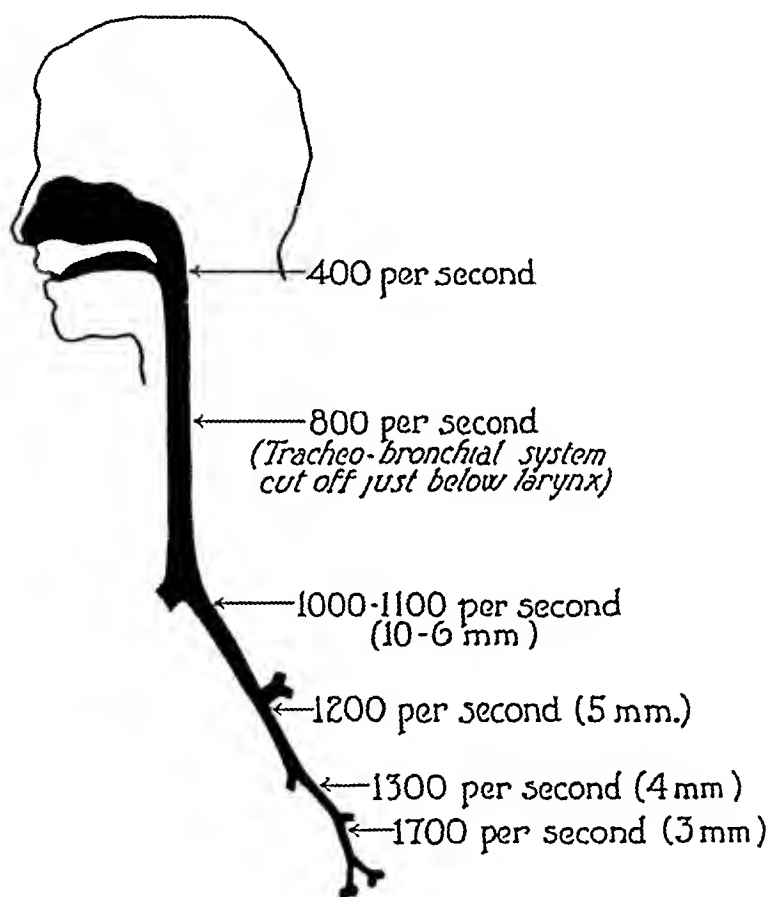


Fig 3—Schematic longitudinal section of tracheobronchial tree with frequency of free vibrations of component tubes as determined by Martini and Mueller (*Deutsches Arch f klin Med* **143** 159, 1923)

burned through, the air in the bronchus was given an impulse, and it vibrated in its own free period or frequency, these vibrations were recorded by the optical capsule on the photographic kymographion.

Figure 3 gives the approximate fundamental frequency of various parts of the tracheobronchial system of adults as determined by Martini and Mueller. The recording T tube was inserted into the bronchus of the diameter shown at various levels, in figure 3, and vibrations of approximately the frequencies inserted in the drawing at these levels were set up in the system by burning through the membrane. In

this illustration it is shown that the tracheal system obtained by cutting off the trachea just below the larynx and inserting the recording apparatus in the distal end has a fundamental frequency of 800 vibrations a second. The bronchial system obtained by cutting off a main bronchus just below the bifurcation has a fundamental frequency of 1,000 vibrations a second. As the periphery is approached, the fundamental pitch of the system becomes higher. The fundamental frequency of the free vibrations of the system is 1,700 a second, if the recording apparatus is inserted into a bronchus of 3 mm internal diameter. Therefore it can be asserted that the bronchial tubes of 3 mm internal diameter or less take no part in the formation of the audible bronchial breath sounds because the lowest free vibration in them is of a pitch much higher than the highest frequency of bronchial breathing as recorded by Martini over areas of consolidation. The fundamental frequency of the system from 4 mm internal diameter peripheriward is also too high to take part in the formation of audible bronchial breath sounds.

From Martini and Mueller's investigations and the acoustic principles previously discussed here it may be concluded that the tracheobronchial breath sounds are formed by the movement of air columns through the tracheobronchial system during breathing, whereby pendulating air movements are formed at bifurcation points and where narrow cross-sections emerge into wider ones. These pendulating air movements are increased in intensity by resonance in the various portions of the pipe system down to bronchi of an internal diameter of from 4 to 5 mm. These intensified air vibrations are the physical basis of the sounds. The fundamental vibration or pitch of the bronchial breath sound is formed in the mouth, nasal cavities and larynx. The overtones which give the sound its characteristic "Klang" are formed in the larger bronchi down to a lumen of 4 to 5 mm diameter.

The sound vibrations produced in the tracheobronchial system must be conducted to the chest wall in order to be auscultated by the physician. The greater part of the sound energy is conducted through the air columns of the bronchial tube system much as the sounds are conducted through the air columns of a stethoscope. A small part of the sound energy enters the walls of the bronchi and the connective tissue in contact with these walls and is conducted along these walls toward the periphery.

Whenever sound vibrations of a given frequency or pitch are impressed on a vibrating system of lower frequency or pitch, there is considerable loss in the amplitude of vibration or intensity of the sound, on the other hand, if the frequency of the second system is greater than that of the first, there is little loss in amplitude or intensity. Therefore as the sound is transmitted along from one system of tubes to the next

with smaller internal diameter but higher frequency, there is little loss of energy from the forcing of the vibration of slower frequency on the system of greater frequency. On the other hand, when the sound reaches tubing of a diameter of 5 mm or less, it is reduced rapidly in intensity because of the friction of the sound in small tubes, as Martini<sup>6</sup> has shown for the conduction of sounds in stethoscope tubing. Schulze<sup>7</sup> has shown that the friction in tubes of 2 mm internal diameter is enormous, and that it is practically impossible to force sound waves through tubing of 1 mm internal diameter. Martini<sup>6</sup> has shown that when a loud sound is sent through a tube of 3 mm internal diameter and only 4 cm length, the intensity is greatly diminished. Under these circumstances, the tracheobronchial breath sounds are not conducted within the tubes farther toward the lung periphery than to the point where the internal diameter of the tubing is 3 mm. At this point most of the sound energy is dissipated as heat through friction.

A small part of the sound energy is conducted along the walls of the bronchi and the connective tissue toward the pleural surface of the lung. This sound energy must to a large extent diffuse through the air sac containing portion of the lung whose fundamental frequency has been determined by Martini to be about from 100 to 150 vibrations a second. The bronchial breath sound vibrations are all much more frequent than this, and much of the intensity of these vibrations is lost when they are necessarily impressed on a system whose vibration period is much slower. It has also been shown experimentally by Sahli, Martini, Montgomery and others that porous lung substance is a poor conductor of the sounds of tracheal breathing. If a piece of normal lung is placed over the trachea, the tracheal sounds are barely heard. Substances like porous lung are good absorbers of sound, whereas consolidated lung is a good conductor of sound vibrations. If a piece of consolidated lung is placed over the trachea, it will be found that the tracheal sounds are fairly well transmitted through the consolidated lung tissue.

Bronchial breath sounds or bronchovesicular breath sounds are heard over the right apex, where large bronchial branches come close to the surface. The small volume of porous lung between these large branches does not completely absorb the bronchial breath sounds, and both faint bronchial breath sounds and the inspiratory vesicular murmur are heard over these areas. The faint, often inaudible expiratory breath sound over areas of the lung is the only part of the bronchial breath sounds that is transmitted to the thorax over these areas.

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6 Martini. Die Schalluebertragung des Stethoskops, *Ztschr. f. Biol.* **53** 117 1920.

7 Schulze. Ueber die Schallgeschwindigkeit in sehr engen Roehren, *Drudes Ann. der Physik*, ser. 4, **13** 1060, 1904.

The inspiratory breath sound is associated with air entering the alveoli, as was shown by Bullar's<sup>3</sup> experiments, mentioned above, and by Sahli,<sup>8</sup> who auscultated a patient with hernia of the lung when the glottis was closed. During expiratory effort under these circumstances, an inspiratory breath sound was heard over the herniated lung, whose air sacs filled during the expiratory effort with a closed glottis.

In order that the typical bronchial breath sounds may be heard, there must be a good conducting contact between the chest wall and bronchi of 3 mm internal diameter or greater. Then the sound waves coming down along the bronchial tubes impinge on the good conducting material. At the surface of the good conducting material, some sound energy is lost by reflection but much is transmitted with only moderately diminished intensity to the thorax wall, where the physician can pick it up with his stethoscope. Consolidated lung tissue is a good conductor of the sounds of bronchial breathing, and normal lung tissue is a poor conductor of sounds of this frequency, as stated in the foregoing. The consolidation must reach from the pleura inward to bronchi of 3 mm diameter or larger, if bronchial breathing is to be heard. The intensity will be greater if the consolidation reaches farther toward the hilum, for then good conducting contact is made with larger bronchi, and the sound energy has been even less dissipated on its way along the tubes. Martini and Mueller<sup>4</sup> have shown that bronchi of 3 mm internal diameter are about 3 cm inward from the pleura in the upper portions of the lung. Bronchi of this caliber are found 3.5-5 cm hilumward from the pleura in the basal and axillary portions of the lung. Bronchi of this bore reach to within 1 to 2 cm of the pleura near the vertebral column. These measurements on cadaver lungs give a good idea of how far a consolidation must extend from the pleura toward the hilum before the faintest bronchial breathing is heard in pneumonia.

The voice sounds are produced by vibrations of the vocal cords, and are modified in intensity and timbre by resonance in the mouth and nasal cavities. These sounds are composed of vibrations of various frequencies, but there are certain characteristic frequencies present in all vowel and consonant sounds no matter what the fundamental pitch is. These frequencies, called formatives, are what characterize the vowel and consonant sounds for our ears. When they are absent, the vowels and consonants do not appear to us to be the vowels and consonants of our spoken language. All the formatives of the vowels and consonants have a pitch much higher than the natural frequency of the porous lung substance (from 100 to 150 a second), with the exception of the formative of *oo*, which has the pitch of *f* on the musical scale and a frequency of 170 vibrations a second, and one of the formatives of *ee*, which has the

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<sup>8</sup> Sahli. Ueber die Entstehung des Vesiculaerathmens, *Cor Bl f schweiz Aerzte* 22 265, 1892

same pitch The voice sounds are conducted down the lumen of the bronchial tubing as well as in the walls of the tubing and the connective tissue surrounding these walls Practically all the energy of the sounds conducted as plane waves within the tubing is dissipated as heat energy when it enters tubes of 3 mm internal diameter No sound energy within the tubes gets farther toward the periphery than tubes of 1 mm internal diameter When auscultation is performed over normal lung, none of the sounds that are conducted within the tubing are heard, but the sound conducted along the walls of the tubing and the interstitial connective tissue gets to the neighborhood of the alveoli with relatively little diminution of its energy The frequency of the porous lung substance, as Mairini<sup>9</sup> has shown, lies between 100 and 150 or thereabouts Sounds of this frequency may be made more intense by resonance in

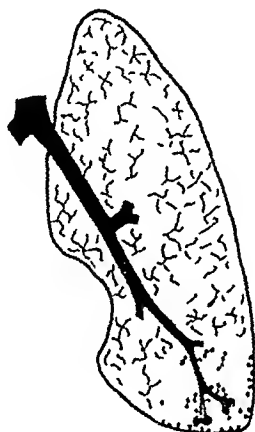


Fig 4—Schematic representation of tracheobronchial tree and lung with lobar pneumonia extending inward to bronchial tubes of 3 mm internal diameter Represents necessary condition for conduction of bronchial breath sounds to thoracic surface

the tissue Sounds of lower frequency lose little energy when impressed on this system of higher frequency Sounds of higher frequency lose energy when impressed on systems of lower frequency, and the farther removed a frequency of higher vibration is from the frequency of the slower system, the greater the loss in intensity of the energy of the more rapid vibration when it is impressed on the slower system For this reason alone the porous lung substance is a poor transmitter of sounds of pitch above  $f$  on the musical scale, or 170 vibrations a second In addition, substances with small air holes dissipate much sound energy through friction in the small pores Therefore, only a little of the voice sound energy reaches the thorax wall, and of this energy only the smallest part is of high pitch The characteristic formatives of the spoken voice sounds are with few exceptions of pitch higher than 170, therefore, the words heard over normal lung are indistinct

Any physician can test out part of these conclusions by having some one with a bass voice sing the notes *c* (130 vibrations) or *f* (170 vibrations) while he palpates the fremitus, then if the singer sounds *c*<sup>1</sup> or *f*<sup>1</sup> or any other note of much higher pitch with the same intensity, the fremitus becomes much less intense. It is hard to get a good, strong vocal fremitus over the lung of women with soprano voices because their lowest notes are above the natural period of their lungs. Part of the energy of the voice sounds conducted down the lumen of the bronchial tubes is reflected and part of the energy of these sounds enters a consolidation, which reaches from the periphery of the lung inward toward the hilum to areas where bronchi of internal diameter of 3 mm are present. This energy is conducted with little loss to the thorax wall except by diffusion, according to the acoustic law of inverse square of the distance from source in isotropic mediums. In addition, the energy conducted along the bronchial walls and connective tissue enters the consolidation and is well conducted to the thorax. A loud sound in which the words are not distinct is heard, and a strong fremitus is felt under these conditions. The words are indistinct because in conduction along the lumen of tubes from 5 to 6 mm bore down to the tubes of 3 mm bore much sound energy is dissipated by friction, and as more of the energy of sounds of higher pitch is lost in friction, the formatives and characteristic overtones are relatively much less strong than in the sound as spoken, therefore, the words are indistinct. The sounds are fairly distinct, and pectoriloquy is present when the consolidation reaches inward to bronchi of 5 to 6 mm bore.

The conclusions have been confirmed experimentally by Martini in his "Habilitationsschrift." He recorded vowel sounds as spoken into his optical recorder and as obtained from the chest wall over normal and consolidated lung. A curve of sound vibrations of fundamental frequency 240 and an overtone of 960 vibrations a second was recorded when the vowel German *u* was spoken directly into the recording instrument (fig 4 b). The sound of 960 vibrations is the formative of German *u*, as determined by Helmholtz many years ago.

The sound as recorded from the chest over normal lung shows only the vibration of 240 a second, the formative has disappeared (fig 5 d). In addition, the intensity of this vibration is much less over the normal chest. The sound recorded over a pneumonic consolidation in the same person shows again the frequency of 240 and 960 vibrations a second, and the relative intensity of the formative is nearly what it was in the sound spoken directly into the instrument (fig 5 c). In addition, the intensity of the fundamental is greater over the consolidation than over the normal lung. We have in this instance an example of pectoriloquy so far as the spoken vowel German *u* is concerned.

Most types of pneumonia begin near the pleural surface, are associated with a pleurisy and progress inward toward the hilum more or less rapidly. A few types of pneumonia in adults may develop centrally and proceed outward toward the pleura. I shall first discuss the types of pneumonia which begin near the pleura. The first stage is a hyperemia soon followed by an exudation of relatively limpid serous fluid. As a rule, the movements of the chest over this area are limited even at this stage. Therefore, less air enters the patent alveoli, and the inspiratory breath sound must be less intense. The serous fluid soon

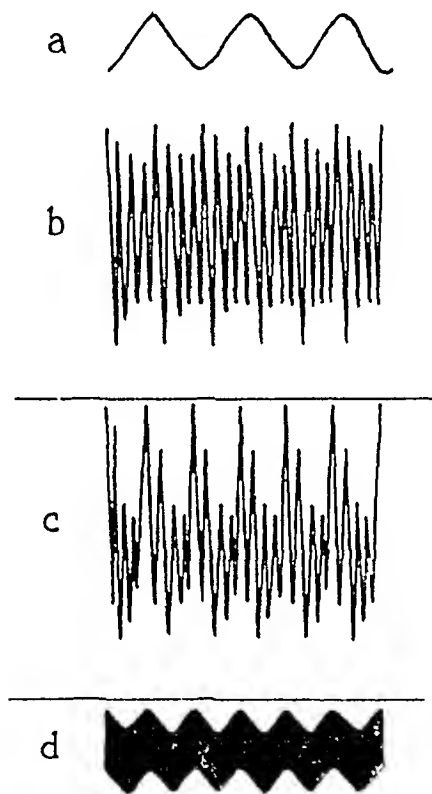


Fig 5—*a* indicates tuning fork vibrations of 110 complete vibrations a second *b*, photographic record of fundamental and formative of German "u" spoken directly into recording apparatus. The fundamental frequency is 240 vibrations a second. Frequency of formative is 960 a second. *c*, photographic record of vibrations over pneumonic consolidation when German "u" is spoken. Formative well represented but relatively less intense than in *b*. *d*, photographic record of vibrations over normal lung of same person when German "u" is spoken. Formative is absent and fundamental is much reduced in intensity. (Reproduction of Martini's curve taken from Martini Studien Ueber Perkussion und Auskultation, Habilitationsschrift, Munchen, 1922.)

becomes more viscous and finally coagulates. The different alveoli will contain fluid in various degrees of viscosity. In some it will be limpid, in others, viscous, and in still others, it will be solid. At this stage crepitant râles will be heard, for they are formed when fluid is present in the finest air passages and in the air sacs themselves. When the fluid gels, crepitant râles cannot be formed. The inspiratory vesicular

murmur becomes faint or disappears entirely, for little or no air enters the air sacs in the pneumonic area now. The expiratory murmur, which is the last rest of the expiratory bronchial breath sound conducted out along the bronchial walls and interstitial tissue, often becomes fainter because when these sound waves enter the pneumonic area, much energy is lost in reflection. The consolidated lung is already a better conductor of sound than the normal porous lung, but because of the various degrees of fluidity of the exudate, and because there may still be some air in the air sacs, many chances for reflection of sound energy are given at the boundaries of materials of different specific gravities and different coefficients of elasticity. For the same reason, the intensity of the spoken voice and tactile fremitus become less in this stage. The energy of the spoken voice sounds is partly reflected at boundaries of different specific gravity and rigidity, and therefore the energy transmitted to the thoracic surface is reduced.

Bronchial breath sounds and bronchophony appear, and tactile fremitus increases in intensity when the consolidated lung reaches inward from the pleura to areas where direct contact is made with bronchi of 3 mm internal diameter or greater. Under these conditions, there is also some sound energy lost by reflection at the boundary of the consolidation, and less is lost when the exudate is coagulated completely. But more of the energy of the breath sounds and voice sounds is now conducted to the pleural surface, because not only part of the energy of the sound conducted along the walls and interstitial connective tissue is transmitted but also part of the much more intense sound energy within the tubing. It is the latter energy which really determines the audibility of the bronchial breath sounds. As the consolidation proceeds inward, it reaches bronchi of 5 to 6 mm bore, the bronchial breath sounds become intense, and pectoriloquy begins to appear, for friction in the tubes has not destroyed much of the energy of the sounds conducted through them until bronchi of this lumen are reached.

Bronchial breath sounds are heard, and bronchophony and tactile fremitus are increased over large volumes of fluid in the chest when this fluid compresses the porous lung substance down to direct contact with bronchi of about 3 mm bore. Under these circumstances the physical signs over fluid are much like those over consolidation, and not infrequently massive exudates in the chest are diagnosed as consolidation when these physical signs are present.

The intensity of the expiratory breath sound varies not a little during the progress of the consolidation from the pleural surface inward. If the pneumonic process is consolidated completely, the exudate firmly gelled, the expiratory breath sound may be prolonged and intense because there is reflection only at one surface and the intensity of the expiratory breath sound has lost less by absorption in the porous lung

substance, because it now passes through less of this porous substance. Moreover, the inspiratory murmur though faint may be suggestive of the bronchial inspiratory breath sound because a small amount of it reaches the consolidation along the walls and interstitial tissue, there being less absorption than in the normal lung, and not a great deal of loss through reflection at the boundary of the consolidation. The breath sounds are then bronchovesicular.

If the pneumonia starts near the hilum, bronchial breath sounds will be heard only when the consolidation reaches the periphery. The same may be said for bronchophony and tactile fremitus. I should assume on theoretical grounds that there would suddenly be intense bronchial breathing and pectoriloquy when the consolidation reached the pleural surface, whereas previously the breath sounds would have been faint, and the voice sounds transmitted normally. There should not be the same gradual transition that obtains when the pneumonic process proceeds hilumward from the pleura. I have never been able to test my assumption experimentally, for I have never seen what I could convince myself was a real central pneumonia during the years that I have been interested in the interpretation of physical signs on a physical basis.

It has often been assumed that absent bronchial breath sounds, tactile fremitus and bronchophony could be explained by a supposed mucous plug in a large bronchus leading to the area. Such a plug would probably lead to the condition of massive collapse, in which, as we know, bronchial breath sounds and increased tactile fremitus may be present. Moreover, this assumption is not necessary, for the absence of bronchial breathing and bronchophony and decrease in tactile fremitus can be explained on the basis of the known facts of pathologic changes and their acoustic consequences. On the other hand, in some cases of lobar pneumonia there is a thin layer of fluid over the area of consolidation, and this fluid may aid in the suppression of the breath sounds, bronchophony and tactile fremitus.

#### CONCLUSIONS

Bronchial breath sounds are formed by the movement of air columns through the bronchial tubes from the larynx to the bronchi of 5 mm internal diameter. The manner of formation is essentially that for the formation of sounds in labial pipes.

The nose, mouth and larynx condition vibrations of a frequency of 400 to 600 a second. The trachea conditions vibrations of a frequency of 800 per second. The main bronchi condition vibrations of 1,000 per second.

These sounds are conducted along the lumen and in the walls and surrounding connective tissue of the walls toward the periphery of the chest. The sound within the lumen is nearly completely obliterated by

friction when tubes of an internal diameter of about 2 mm are reached. Only part of the sound energy of the expiratory bronchial breath sound reaches the thorax wall, being conducted along the walls of the tubes and through the strongly absorbing porous substance of the alveolar structure.

Bronchi with an internal diameter of 3 mm are 3 cm from the pleural surface in the upper lobes and 3.5 to 5 cm from the pleural surface in the lower lobes except near the vertebral column where they are only from 1 to 2 cm from the periphery.

Consolidation must reach inward this far in order to make good conducting contact with bronchial tubes of 3 mm bore and thus conduct bronchial breath sounds to the wall of the thorax in pneumonia.

The first physical signs of pneumonia obtained on auscultation are crepitant râles, diminished or absent breath sounds and diminished spoken voice. Tactile fremitus is also diminished at a time when the consolidation has not reached bronchi of 3 mm internal diameter.

There are bronchial breathing and bronchophony and a stronger fremitus when bronchi of this diameter are surrounded by consolidation reaching to the periphery.

Pectoriloquy appears when the consolidation reaches in to around bronchi of 5 to 6 mm internal diameter.

The spoken vowel sound over normal lung area contains only the fundamental frequency of the vowel sound. The condition of pectoriloquy is obtained when the vowel sound is so well conducted to the chest wall that the sound contains the formatives as well as the fundamental frequency of the vowel sound. Bronchophony is the condition in which the fundamental frequency is better transmitted to the periphery and thus louder, but the formative or formatives are not well transmitted, and therefore the vowel is not distinct, only louder than when heard over normal lung area.

# RELATION OF HEMOGLOBIN, CELL COUNT AND CELL VOLUME TO THE ERYTHROCYTE SEDIMENTATION REACTION\*

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In explaining the erythrocyte sedimentation reaction the majority of investigators have limited themselves to the study of the physico-chemical changes that occur in the plasma and have paid little attention to the erythrocytes. The few attempts made to study the latter have been on citrated or oxalated blood. These anticoagulants, however, as will be shown later, so alter the quantitative relationship between the plasma and the cells as to render their use unsuitable for the study of the erythrocytes. The use of hirudin offers the best available means of keeping the blood in fluid condition without otherwise changing its composition. Its recent use by Gram and Norgaard<sup>1</sup> for the determination of standards of hemoglobin, cell count and cell volume for healthy persons suggested its employment in studying the same factors in conjunction with the sedimentation reaction.

## METHODS

Specimens of blood were obtained before breakfast from ten healthy adults (physicians and nurses) and thirty patients in the following manner:

1 *Sedimentation Reaction*—Into a sterile 2 cc record syringe, a solution of 3.8 per cent sodium citrate was drawn to the 0.4 mark. With a tourniquet applied loosely above the elbow so as not to occlude the radial pulse, blood was aspirated from an arm vein to the 2 cc mark, giving a dilution of 1:4. The syringe was then removed and, with the needle left in situ, about 5 cc of blood was collected in a small bottle containing 1 mg of powdered hirudin. The blood was thoroughly mixed. Citrated blood and duplicate samples of hirudinized blood were then drawn into 1 cc serologic pipets approximately 20 cm in length and graduated into hundredths. These were placed vertically in a specially constructed stand and kept firmly pressed by means of rubber bands on a rubber mat covering the base of the stand. The extent of

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\* From the Montefiore Hospital for Chronic Diseases.

1 Gram, H C, and Norgaard, A. Relation Between Hemoglobin, Cell Count and Cell Volume in Venous Blood of Normal Human Subjects. Arch Int Med **31** 164-170 (Feb) 1923.

sedimentation was noted at the end of one, two and twenty-four hours and the results read directly in percentage as recommended by Morriss<sup>2</sup>

2 *Hemoglobin*—On each specimen of hirudinized blood three determinations were made with a Sahli hemoglobinometer containing colored glass comparison rods. The hemoglobin percentage was calculated on the assumption that 100 per cent hemoglobin equals 5 millions of normal red blood cells so as to give a color index of 1. Gram and Norgaard<sup>1</sup> have shown that such a calculation differed on an average of 0.56 per cent from that obtained by correcting the hemoglobinometer to read on the basis of 100 per cent hemoglobin having an oxygen combining capacity of 18.5 per cent by volume. As a further check, however, the Sahli standard was compared with a standardized hemoglobin solution. The two methods checked closely.

3 *Cell Count*—Two counts from separate pipets were made on each specimen of hirudinized blood. A Neubauer counting chamber and Haymen's diluting fluid were used for counting the cells. When differences between counts were greater than 200,000 cells, a third count was done.

4 *Cell Volume*—Cell volume percentage was obtained with the use of Van Allen's<sup>3</sup> hematocrits. Four determinations on the blood of the controls and duplicate determinations on the blood of the patients were made. The tubes were centrifugalized for one to one and one-half hours at a rate of 2,400 revolutions per minute, the longer time being taken for the blood of the controls. The final readings did not include the layer of white blood cells. Variations that occurred between readings rarely exceeded 0.5 per cent.

## RESULTS

The results will be discussed in the order in which they are tabulated.

Table 1 represents the data for ten normal subjects, five men and five women, with the comparative results of Gram and Norgaard. We obtained an average erythrocyte count of approximately 5 million cells as contrasted to the higher count of these authors and, as one would expect, our hemoglobin percentage is nearer 100. The volume index agrees closely with theirs, while the cell volume averages differ only by 0.66 per cent. Somewhat greater discrepancies are seen in comparing the data on the women, our averages being generally lower with the exception of that obtained on cell volume. It is quite possible that a larger group of controls would have compared more closely. The data listed in the remaining columns will be referred to in the general discussion of the results.

2 Morriss, W. H. The Value of Erythrocyte Sedimentation Determinations in Pulmonary Tuberculosis, *Am Rev Tuberc* 10 431-440 (Dec.) 1924.

3 Van Allen, C. M. An Hematocrit Method, *J Lab & Clin Med* 10 1027-1040 (Sept.) 1925.

1 *Hemoglobin*—The hemoglobin content of the red blood cells parallels to a certain degree the erythrocyte sedimentation reaction. However, there are a number of instances in which high hemoglobin percentages accompanied increased sedimentation as well as cases in which relatively low hemoglobin percentages accompanied normal sedimentation. In general, our results agree with those of Groedel and Hubert<sup>4</sup> who found that the lower the hemoglobin content of the blood the more frequently is increased sedimentation obtained and that the hemoglobin per se is not directly related either to the two or the twenty-four hour sedimentation values.

TABLE 1—Results of Blood Tests of Ten Normal Subjects

	Number	Age	Hemoglobin, per Cent	Cell Count, Millions per C Mm	Volume Index	Cell Volume, per Cent (Hematocrit)	Sedimentation Reaction on Hirudinized Blood, per Cent		Cell Volume, per Cent (Spontaneous)	Cell Volume (Spontaneous) Minus	Cell Volume (Hematocrit)	Cell Volume (Hematocrit)	Cell Volume (Spontaneous)	2-Hour Reading	24 Hour Reading
							2	24							
							Hrs	Hrs							
Normal males	1	25	106	5 600	0.97	51.0	2.0	29.5	70.5	19.5	0.72			6.8	
	2	25	110	5 250	1.03	50.5	3.5	32.5	67.5	17.0	0.75			10.8	
	3	25	100	4 750	1.05	47.0	6.0	35.0	65.0	18.0	0.72			17.1	
	4	25	84	4 570	0.91	40.0	10.5	39.5	60.5	20.5	0.66			26.6	
	5	25	100	4 900	1.00	46.5	13.0	41.0	59.0	12.5	0.79			31.7	
Average			100	5 010	1.00	47.0	7.0	35.5	64.5	17.5	0.73			18.6	
Maximum			110	5 600	1.05	51.0	13.0	41.0	70.5	20.5	0.79			31.7	
Minimum			84	4 550	0.91	40.0	2.0	29.5	59.0	12.5	0.66			6.8	
Gram and Norgaard (10 Cases)															
Average			108.32	5 454	1.00	46.34									
Maximum			117.26	5 911	1.03	50.00									
Minimum			95.62	4 854	0.96	42.38									
Normal females	6	35	81	3 750	1.14	40.0	10.0	41.5	58.5	18.5	0.68			24.1	
	7	21	84	3 650	1.24	42.5	12.0	44.5	55.5	13.0	0.77			26.9	
	8	23	82	4 200	1.08	42.5	21.0	46.0	51.0	11.5	0.79			15.7	
	9	23	94	4 100	1.10	42.5	20.0	46.0	54.0	11.5	0.79			43.5	
	10	22	87	4 100	1.12	43.0	22.5	46.0	54.0	11.0	0.80			48.9	
Average			86	3 930	1.13	42.1	17.1	44.8	55.2	13.1	0.77			37.5	
Maximum			94	4 200	1.24	43.0	22.5	46.0	58.5	18.5	0.80			48.9	
Minimum			82	3 650	1.08	40.0	10.0	41.5	54.0	11.0	0.68			24.1	
Gram and Norgaard (10 Cases)															
Average			93.85	4 654	1.01	40.33									
Maximum			101.68	5 054	1.06	43.00									
Minimum			87.49	4 360	0.97	38.81									

2 *Cell Count*—What has been stated regarding the relationship of hemoglobin to the sedimentation reaction applies equally to the cell count. The patients in this series had chronic diseases with varying degrees of secondary anemia so that with the decrease in cell count there was a proportional decrease in the hemoglobin content.

4 Groedel, F. M., and Hubert, G. Die Blutkörperchensenkungsgeschwindigkeit bei inneren Erkrankungen, besonders bei Kreislaufstörungen. *Ztschr. f. klin. Med.* 192 31-46 (April) 1925.

TABLE 2—Results of Blood Tests of Patients

Number	Age	Sex*	Clinical Diagnosis	Hemoglobin, per Cent	Cell Count, Millions per C Mm	Volume Index	Cell Volume, per Cent (Hematocrit)	Sedimentation Reaction on Hirudinized Blood, per Cent		Cell Volume, per Cent (Spontaneous)	Cell Volume (Spontaneous) Minus	Cell Volume (Hematocrit)	Cell Volume (Hematocrit)	Cell Volume (Spontaneous)	2-Hour Reading $\times 100$	24 Hour Reading
								2 Hrs	24 Hrs							
11	47	♂	Multiple sclerosis	107	5 200	1 02	50 0	17 5	38 5	61 5	11 5	0 81	45 4			
12	58	♂	Resection of cancer of rectum, no evidence of recurrence	98	4 150	1 24	48 5	12 5	39 0	61 0	12 5	0 79	32 0			
13	17	♂	Chronic rheumatic heart disease	102	4 750	1 06	47 5	11 5	41 5	58 5	11 0	0 81	27 7			
14	57	♂	Chronic arthritis	90	4 500	1 12	47 5	13 0	42 0	58 0	10 5	0 82	30 9			
15	52	♂	Cancer of stomach	105	4 900	1 08	50 0	28 0	43 5	56 5	6 5	0 88	64 4			
16	60	♂	Generalized arterio sclerosis	101	5 000	1 01	47 5	27 5	43 5	56 5	9 0	0 84	63 2			
17	76	♂	Generalized arterio sclerosis	89	3 950	1 32	49 0	24 0	44 0	56 0	7 0	0 88	54 5			
18	39	♀	Paralysis agitans (postencephalitic)	80	4 100	1 11	43 0	13 5	44 0	56 0	13 0	0 77	30 7			
19	49	♂	Chronic pulmonary tuberculosis	88	3 800	1 23	44 0	37 0	46 0	54 0	10 0	0 81	80 4			
20	20	♀	Chronic pulmonary tuberculosis	88	4 200	1 07	42 5	39 0	49 0	51 0	8 5	0 83	79 6			
21	46	♂	Endothelioma of right pleura with skeletal metastases	87	4 750	0 96	43 0	41 5	49 5	50 5	7 5	0 85	83 8			
22	64	♀	Cancer of bladder	88	4 100	1 06	41 0	35 0	51 0	49 0	8 0	0 84	68 6			
23	39	♀	Paralysis agitans (postencephalitic)	81	3 750	1 15	40 5	45 5	52 0	48 0	7 5	0 84	87 5			
24	64	♂	Chronic osteomyelitis of left femur	77	4 150	1 05	41 0	42 0	52 5	47 5	6 5	0 86	80 0			
25	56	♂	Tabes dorsalis	88	4 150	0 97	38 0	43 5	53 0	47 0	9 0	0 81	82 1			
26	37	♂	Paralysis agitans (postencephalitic)	79	3 600	1 15	39 0	33 0	53 0	47 0	8 0	0 83	62 3			
27	69	♀	Cancer of external genitalia	86	3 600	1 21	41 5	48 0	53 0	47 0	5 5	0 88	93 0			
28	30	♂	Chronic pneumonitis with adherent pleura	70	4 300	0 91	37 0	43 5	54 5	45 5	8 5	0 81	79 8			
29	52	♂	Chronic pulmonary tuberculosis	74	3 550	1 09	36 5	46 0	55 5	44 5	8 0	0 82	82 9			
30	29	♀	Myelitis due to Pott's disease	80	3 600	1 11	37 5	50 0	56 0	44 0	6 5	0 85	89 3			
31	32	♀	Infectious polyarthrit	76	3 750	1 08	38 0	52 0	56 5	43 5	5 5	0 87	92 0			
32	61	♀	Undiagnosed	81	3 350	1 17	37 0	44 5	58 0	42 0	5 0	0 88	76 7			
33	60	♀	Cancer of breast with metastases to lung	77	3 800	1 05	37 5	53 5	58 0	42 0	4 5	0 89	92 2			
34	65	♀	Basal cell epithelioma of lip with bone necrosis	84	4 000	0 96	34 0	53 0	58 0	42 0	8 0	0 81	91 4			
35	37	♀	Cancer of breast with skeletal metastases	81	4 000	0 93	35 0	56 0	59 5	40 5	5 5	0 86	94 1			
36	63	♂	Cancer of esophagus	80	3 550	1 05	35 0	55 0	60 0	40 0	5 0	0 88	91 7			
37	21	♀	Advanced pulmonary tuberculosis	66	3 800	0 92	33 0	58 0	62 0	38 0	5 0	0 87	93 5			
38	40	♂	Cancer of colon	52	2 150	1 33	27 0	63 0	68 0	32 0	5 0	0 84	92 6			
39	62	♀	Cancer of colon	45	2 100	1 06	21 0	72 0	75 0	25 0	4 0	0 84	96 0			
40	70	♂	Cancer of bladder	44	2 150	0 94	19 0	74 0	76 5	23 5	4 5	0 81	96 7			

\* In this and table 3, ♂ indicates male, ♀ female

3 *Volume Index*—The volume index was calculated by dividing the cell volume by the red count in millions per cubic millimeter and multiplying this by the factor 0.1066 in order to obtain 1.0 as the normal volume index. This index shows no significant relationship to the erythrocyte sedimentation reaction. The color index also was calculated and was found to parallel the volume index to some extent.

4 *Cell Volume*—The cell volume is an expression of the cell count and the hemoglobin content of the cells and is an excellent check on them. When the cell volume readings are compared with the sedimentation reaction, the relationship between the two, especially the twenty-four hour readings of the latter, is quite striking. It will be noted that with a decrease in cell volume there is a proportional increase in the twenty-four hour reading. Since the sedimentation results are expressed in plasma percentage rather than in terms of cells, column 7 is inserted to show this relationship on a comparative basis. In other words, the cell volume obtained by hematocrit bears a fixed ratio to that obtained by the spontaneous settling of the cells in twenty-four hours, which represents approximately the limit to which the cells can settle. In the subsequent two columns this fact is illustrated more clearly. Thus, in spite of the greater differences between the spontaneous and centrifugal settling of the cells that occurs in the blood showing normal or moderate sedimentation, and represented in column 8, the ratio  $\frac{\text{cell volume per cent (hematocrit)}}{\text{cell volume per cent (spontaneous)}}$  averages 83.9 for the patients and 74 for the controls. The lower factor of the healthy controls is in itself of some interest. From it we deduce that the red blood cells of healthy persons possess a greater faculty of remaining in suspension than the blood of patients. This may be another expression of the relative stability of the blood in health. That this occurs in spite of cell volume percentages that are frequently lower than that in patients' blood adds greater significance to this finding.

The two hour readings do not bear as close a relationship to the cell volume as do the twenty-four hour readings, although there is a distinct tendency for them to do so. This we believe is due to the fact that in the early hours of sedimentation two forces are at work, the plasma and the cells. In a previous article one of us<sup>5</sup> has shown that both plasma and serum show increasing ability of precipitation on the addition of various reagents, and that this characteristic of the plasma and serum paralleled the erythrocyte sedimentation reaction. It may be assumed, therefore, that in the early hours of sedimentation there is greater freedom of interplay between plasma and cells but that as

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5 Rubin, E. H. Relation of the Erythrocyte Sedimentation Reaction to the Ability of Flocculation of the Plasma and Serum, *Arch. Int. Med.* **37**:848 (June) 1926.

sedimentation progresses the mechanical force exerted by the cells becomes increasingly greater until, in time, the reaction becomes predominantly an expression of cell volume. We have devised the ratio  $\frac{\text{two hour sedimentation per cent}}{\text{twenty four hour sedimentation per cent}}$  to express the relationship existing between plasma and cells at periods when they exert their greatest influence on sedimentation. This index has the advantage over the two hour reading alone, which is generally employed, because it takes into consideration such cases in which a normal corpuscular volume exists in the presence of a pathologic condition of the tissue as well as cases in which the degree of anemia is out of proportion to the severity of tissue destruction. Both types of cases are frequent.

Applying the index thus obtained to the forty cases studied we find all the normals and five patients giving values below 50, that is, the sedimentation at two hours is less than one-half that occurring in twenty-four hours while the remaining twenty-five patients have values over 50, of which ten are over 90.

#### EFFECT OF ANTICOAGULANTS ON CELL VOLUME

The difficulty of demonstrating a relationship between the sedimentation reaction and the cell volume with the use of citrates or oxalates is easily explained and has been recognized by Westergren<sup>6</sup> and several others. Thus, for example, when the usual dilution of 1 part sodium citrate is added to 4 parts of whole blood containing 50 per cent cells, the cells become only 40 per cent of the citrated blood, with a loss of 10 per cent, if, however, the cells make up only 20 per cent of the blood volume, the cells become reduced to 16 per cent of the citrated blood, with a loss of 4 per cent. The determination of cell volume on citrated blood is therefore erroneous unless the factor of dilution is taken into consideration, assuming that the diluent is isotonic with blood. A preliminary study of forty-six cases convinced us of the inaccuracy inherent in such a method. The tendency, however, for increased sedimentation to accompany low cell volume was so evident grossly that it seemed desirable to study the question further.

With the use of salts to prevent coagulation, changes are produced in the osmotic pressure of the blood which cause considerable alteration in the size of the cells. Hooper, Smith, Belt and Whipple<sup>7</sup> have shown that the addition of sodium oxalate crystals in minimal amounts capable of preventing coagulation (0.1 per cent) will cause on an average a shrinkage in the cell volume of about 3 per cent, while Van Allen<sup>8</sup> found the change to be 5.5 per cent. We have found the shrinkage to vary

<sup>6</sup> Westergren, A. Die Senkungsreaktion, *Ergebn d inn Med u Kinderh* 26 577-732 (April) 1924.

<sup>7</sup> Hooper, C W, Smith, H P, Belt, A E, and Whipple, G H. Blood Volume Studies, *Am J Physiol* 51 205-220 (March) 1920.

somewhat with the cell volume, the greater the cell volume the greater being the shrinkage, as compared to the cell volume obtained on hirudinized blood. Since it is customary to add an excess of the oxalate in actual practice, this source of error becomes much larger. Table 3 represents four simultaneous cell volume determinations on hirudinized, citrated and oxalated blood to illustrate the matter under discussion.

Using graded amounts of citrate solution to compensate for variations in cell volume, Bonniger and Herrmann<sup>8</sup> were able to show a relationship between the sedimentation reaction and the cell volume. The use of hirudin in our experiments simplified matters by dispensing with extraneous diluents. The action of hirudin in preventing coagulation is yet to be determined but it is certain that for our purpose it offered an excellent means of studying the problem.

#### EFFECT OF DILUTION AND CONCENTRATION ON THE SEDIMENTATION REACTION

The relationship that exists between cell volume and the sedimentation reaction can be demonstrated also by changing the proportion of plasma to cells. This is easily done by adding or subtracting definite

TABLE 3—*Effect of Anticoagulants on Cell Volume*

Num- ber	Age	Sex	Clinical Diagnosis	1 Mg Hirudin in 5 Cc Blood, Hematocrit	1:4 Dilution with 3.8 per Cent Sodium Citrate Solution, Hematocrit	5 Mg Sodium Oxalate in 5 Cc Blood Hematocrit
				Cell Volume, per Cent	Cell Volume, per Cent	Cell Volume, per Cent
1	47	♂	Multiple sclerosis	51	38	48
2	57	♂	Chronic arthritis	44.5	31.5	41.5
3	40	♀	Pulmonary tuberculosis	35	24.5	33
4	70	♂	Cancer of bladder	20	15.5	20

amounts of homologous plasma and determining the cell volume on the modified samples by hematocrit. The method besides being simple has the further advantage of keeping the original cell volume intact. In view of the work of Abderhalden<sup>9</sup> who found that the various layers of erythrocytes differ in their sedimenting properties, this precaution was worth taking.

#### PROTOCOLS

EXPERIMENT 1—The hirudinized blood of a control was divided evenly into four small test tubes. On one of these A1, the routine sedimentation, cell volume, hemoglobin and cell count determinations were made. The blood in

<sup>8</sup> Bonniger, M., and Herrmann, W. Blutkörperchen-Senkungsgeschwindigkeit und Volumen, Klin. Wchnschr. 2:744-745 (April) 1923.

<sup>9</sup> Abderhalden, E. Weitere Forschungen über die Senkungsgeschwindigkeit der roten Blutkörperchen bei gleichen und bei verschiedenen Tierarten und unter verschiedenen Bedingungen (II Mitteilung), Pflüger's Arch. f. d. ges. Physiol. 193:236-280, 1922.

the remaining three tubes was allowed to sediment spontaneously and when the cells had settled sufficiently to show clear plasma, 0.35 cc of plasma was removed from one tube, A4, and immediately added to a second tube, A3. On these modified samples, as well as on the fourth sample that served as a control, the same determinations were made as on the first. Frequent readings were taken to plot the results.

It was noted that when plasma was added to tube A3 thereby producing a relative decrease in cell volume there followed an increased sedimentation, that tube A4 in which the cell volume was relatively increased gave a reaction above normal, and that tube A2, the control, gave approximately the same sedimentation as the original, A1.

EXPERIMENT 2—The same procedure used in experiment 1 was carried out on the blood of a tuberculous patient showing an increased sedimentation reaction. B1 is the sedimentation graph of the original blood, B2 and B3, from which 0.5 and 0.75 cc samples of plasma were removed, respectively, while B4 represents the graph of a sample of blood diluted with 1 cc of plasma.

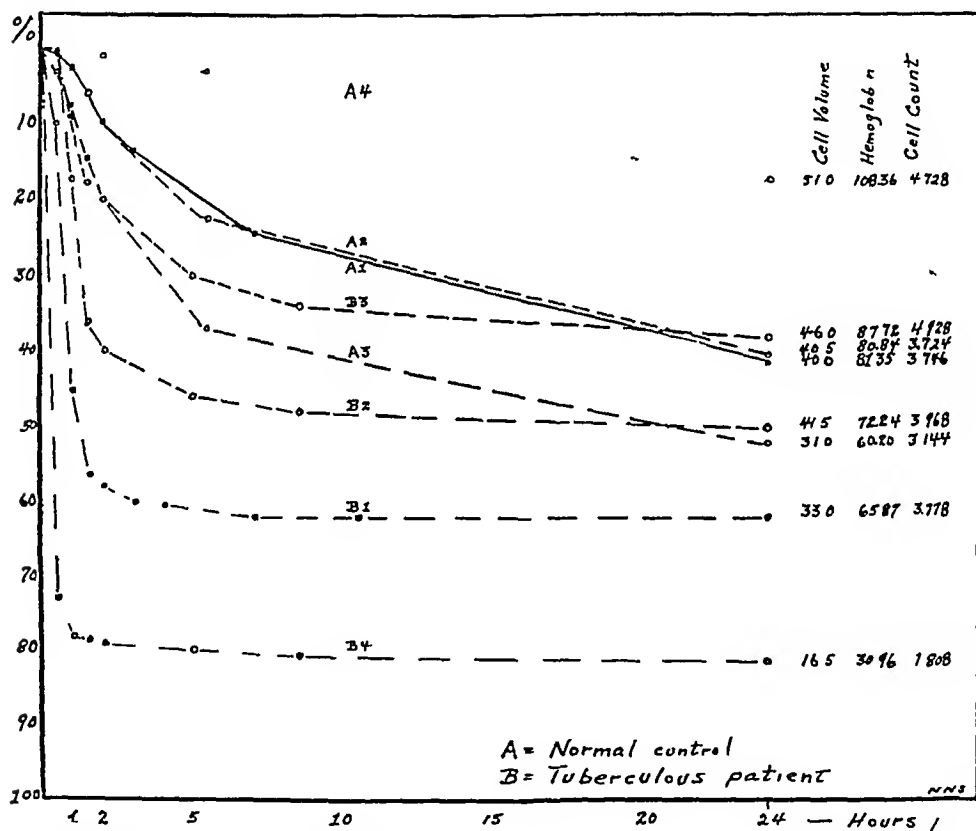


Chart 1—Effect of dilution and concentration on the sedimentation reaction

Depending on the degree of dilution or concentration of the erythrocytes, a relative increase or decrease in the sedimentation reaction was obtained. The changes affected the two hour as well as the twenty-four hour readings. The hemoglobin percentages and cell counts roughly followed the alterations in cell volume.

These experiments were repeated. The results substantiate our previous opinion regarding the relationship of plasma to cells and the desirability of combining both factors in some such manner as we have indicated.

Clinically, it is well known that in conditions associated with polycythemia a delay is found while marked anemia causes an increase in the sedimentation reaction. In view of our results, we believe that the volume of erythrocytes exerts an important influence on the sedimentation reaction under all conditions, and that possibly physiologic changes in sedimentation are also to a great extent influenced by the erythrocyte factor. Thus, the lower cell volume percentage found in women would

TABLE 4—*Comparison of Sedimentation Between Citrated and Heparinized Blood*

Case	Two Hour Sedimentation, per Cent			Twenty-Four Hour Sedimentation, per Cent		
	Citrated Blood	Heparinized Blood	Difference	Citrated Blood	Heparinized Blood	Difference
1	10	20	—100	18.5	29.5	—110
2	17.5	35	—175	22.5	32.5	—100
3	25	60	—35	27.0	35.0	—80
6	60	100	—40	40.5	41.5	—10
13	60	115	—55	35.5	41.5	—60
4	70	105	—35	40.5	39.5	+10
12	70	125	—55	32.0	39.0	—70
9	75	200	—125	40.0	46.0	—60
14	75	130	—55	34.5	42.0	—75
5	80	130	—50	35.0	41.0	—60
11	80	175	—95	34.5	38.5	—40
18	80	135	—55	39.0	44.0	—50
7	100	120	—20	41.0	44.5	—35
17	100	240	—140	38.0	44.0	—60
8	130	210	—80	42.0	46.0	—40
10	150	225	—75	46.0	46.0	±00
15	150	280	—130	44.0	43.5	+05
16	160	275	—115	42.5	43.5	—10
26	200	330	—130	50.0	53.0	—30
22	260	350	—90	56.5	51.0	+55
32	265	445	—180	56.5	58.0	—15
25	290	435	—145	55.0	53.0	+20
30	350	500	—150	61.0	76.0	—150
20	380	390	—10	60.0	49.0	+110
27	400	480	—80	60.0	53.0	+70
33	410	535	—125	65.0	58.0	+70
34	480	530	—50	65.0	58.0	+70
23	490	455	+35	65.0	52.0	+130
31	500	520	—20	65.5	56.5	+90
19	530	370	+160	63.0	46.0	+170
28	530	435	+95	65.0	54.5	+105
24	535	420	+115	67.0	52.5	+145
38	540	630	—90	74.0	68.0	+140
35	550	560	—10	68.5	59.5	+90
36	550	550	±00	69.5	60.0	+95
21	560	415	+145	64.0	49.5	+145
29	600	460	+140	68.0	55.5	+125
39	650	720	—70	78.5	75.0	+35
37	685	580	+105	72.0	62.0	+100
40	820	740	+80	84.0	76.5	+75

explain the greater sedimentation reactions that they give in comparison to men. The clinical value of the sedimentation reaction in surgery has been reviewed by one of us<sup>10</sup> in another article and a micromethod<sup>11</sup> described to facilitate a wider application of the test.

10 Rubin, E. H. The Clinical Value of the Erythrocyte Sedimentation Reaction in Surgery, *Surg Gynec Obst* **42** 652-656 (May) 1926

11 Morriss, W. H., and Rubin, E. H. The Sedimentation Reaction of Erythrocytes. Clinical Applications and a Micromethod, *J Lab & Clin Med* **11** 1045-1052 (Aug) 1926

COMPARISON OF SEDIMENTATION BETWEEN CITRATED AND  
HIRUDINIZED BLOOD

In table 4 are arranged the two and twenty-four hour readings on the citrated and hirudinized blood. The one hour reading is omitted because of the inaccuracy in taking readings on a rapidly sedimenting blood at this time.

Table 4 shows that approximately up to the 15 per cent reading on the citrated column the hirudinized blood settles more rapidly and maintains its lead to the end of the twenty-four hours. From the 15 to the 29 per cent reading, the twenty-four hour results show occasionally a greater sedimentation of the citrated blood and that above the 29 per cent reading the citrated blood had definitely outpaced the hirudinized blood.

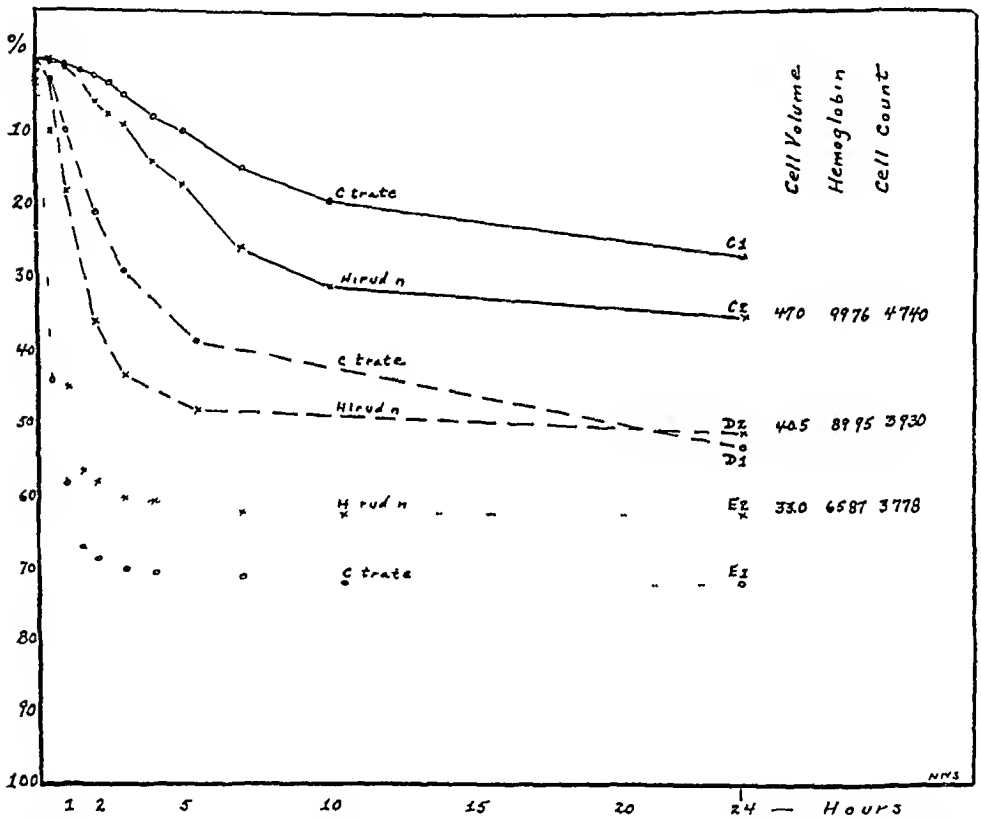


Chart 2—Relation between sedimentation reaction on citrated and hirudinized blood

at some period between the second and the twenty-fourth hour. Above the 50 per cent reading we note that in many instances as early as the second hour, the citrated blood had settled faster and had retained its lead over the hirudinized blood throughout the twenty-four hours.

This relationship is made clearer in chart 2.

To interpret this apparently paradoxical relationship of the citrated to the hirudinized blood, we have the following explanation to offer, which however, is an hypothesis.

When sodium citrate is added to make a dilution of 1 : 4 of blood that contains, let us assume, 50 per cent plasma and 50 per cent cells, the plasma and the cells are diluted the same amount, each forming two-fifths of the entire mixture. Such a relationship might exist when citrate is added to blood with a normal cell volume. The diluent, if isotonic, produces relatively little change on the cells in comparison to the effect it exerts on the plasma. If the plasma has low precipitating ability, as is usually the case in normal blood, the additional citrate is sufficient to reduce this power to some degree with consequent neutralization of whatever action it may exert on the cells. The hirudinized blood, on the contrary, unaffected by diluent acts in maximum intensity and causes a greater sedimentation of the cells.

If, however, the blood contains 75 per cent plasma and 25 per cent cells, on the addition of citrate in the dilution of 1 : 4 the plasma is converted to three-fifths of the entire mixture and is therefore in a relatively more concentrated form than in the case previously described. Such a plasma would have greater precipitating power on a mathematical basis. In reality, we find the plasma in these cases to possess much greater ability of precipitation than normally. This would manifest itself in increased sedimentation.

The cell volume is affected by the addition of diluent in the following manner. In the first case, the modified plasma acts on cells totaling two-fifths of the entire mixture, in the second case, on cells totaling only one-fifth of the entire mixture. Thus, we have a relatively less concentrated plasma acting on a greater cell volume in the first case and just the reverse in the second case although the citrate is added to both in the same proportion. This fact, in our opinion, is sufficient to account for the greater sedimentation occurring in the latter instance. A consideration of these two factors might help explain the differences observed between the sedimentation of the citrated and the hirudinized blood and to a certain degree the mechanism of sedimentation in the former. We are assuming that the hirudin, itself, is not playing a significant part in the reaction aside from its action as an anticoagulant.

#### SUMMARY

- 1 The erythrocyte sedimentation reaction was studied on hirudinized blood.

- 2 This method obviates such complicating factors as dilution and osmotic pressure changes that are inherent in the methods employing citrates or oxalates to prevent coagulation.

- 3 With the use of hirudinized blood, a close relationship was found to exist between the erythrocyte sedimentation reaction and the cell volume as determined by hematocrit, the lower the cell volume, the greater being the rapidity of sedimentation.

4 By artificially decreasing the cell volume normally sedimenting blood could be made to settle more rapidly. Conversely, by increasing the cell volume, rapidly sedimenting blood could be made to approach normal limits.

5 Comparative results with hirudinized blood showed that the use of 3.8 per cent sodium citrate solution as an anticoagulant in the dilution of 1:4 of blood gave inconstant readings in the sedimentation reaction. These changes seemed referable to the effect of the diluent on the plasma and the cells.

6 The stability of hirudinized blood seems better expressed by the ratio  $\frac{\text{two hour}}{\text{twenty four hour}}$  reading than by the two hour reading alone, as this ratio expresses the relationship of plasma to cells at periods when they exert their greatest influence on sedimentation.

## Book Reviews

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AVIATION MEDICINE LOUIS HOPEWELL BALIR, M D, Major, M C, U S A,  
Commandant of the School of Aviation Medicine Price, \$7 50 Pp 241  
Baltimore Williams & Wilkins Co, 1926

With the great development of aviation during the late war, it became necessary for the advancement of aviation as a military measure and for the safety of those engaged in it, to study the physical requirements for successful flying and for the performance of the various military duties required. This demanded a thorough study of the physiologic response to altitude. To accomplish this the government maintained a research laboratory in which a large amount of work was done on the physiologic response to altitude, visual requirements for flying, the mechanism of equilibration, the psychologic reactions under different conditions, reaction time and the various bodily requirements. In addition, the experiences in the flying fields in this country and abroad and in the combat zone were collected and analyzed.

In the course of such investigations, it was inevitable that important contributions should be made to our fundamental knowledge. All of this material has been available to the author, who has been commandant at the School of Aviation Medicine since shortly after the armistice, and to whose wise direction much of the credit for the work accomplished should be given.

The book is primarily a text for aviation surgeons and for those interested in civilian aviation, and as such is of exceptional value. It is much more than that, however, and is valuable to those interested in every branch of medicine. While the results of investigation and experience here and abroad must be considered briefly at times, full references are given to the original literature.

The general physical needs are considered, followed by chapters on the visual requirements, the nose, throat and ear, psychologic requirements, reaction time and methods for testing the applicant. A full section is devoted to the physiology of aviation, especially the effect of altitude on the circulation and respiration and the methods by which the body compensates, the psychologic effects of altitude, and methods for determining the reaction of the applicant to altitude. In a section of several chapters the care of the aviator is discussed, with chapters on fatigue, staleness, protective devices and a chapter devoted to airplane accidents. A final chapter is devoted to civilian aviation. Details of tests and examination with specimen charts are given in a supplement.

A complete bibliography adds to its great value as a text and book of reference.

DIE ELEKTROGRAPHIE, UND ANDERE GRAPHISCHE METHODEN IN DER KREISLAUF-DIAGNOSTIK DR ARTHUR WEISS, A O Professor in der Universität  
Giessen Price, 19 marks Pp 208, with 139 illustrations Berlin Julius  
Springer, 1926

This volume is a compact and a thorough exposition of methods for the graphic registration of the phenomena associated with the heart beat, and as a text and book of reference, it fills a place not filled by any one book in English. The apparatus necessary for the establishing of a laboratory for the investigation of heart disease is considered in general. The Frank capsule photographic registration and application to the registration of the venous or arterial pulse, respiration, or the heart sounds. The electrocardiograph and its use are described in some detail.

The bulk of the book deals with the results which may be obtained by the use of the apparatus described and with what may be learned from the results. The normal observations are described and the deviations from normal in different physiologic and anatomic conditions. The arrhythmias are given

under a classification based on the properties of heart muscle as described by Hering, such as disturbances of stimulus production, of stimulus conduction, of excitability and of contractility, and the observations by all the methods of investigation described are considered. The pathologic background, experimental production, physiologic theories and clinical significance are discussed. Auricular fibrillation is discussed under the heading "Disturbances of Stimulus Conduction," as arrhythmia absoluta. As is warranted by its relative importance, more space is given to the theories of its production than to the other arrhythmias. Pulsus alternans is presented under "Disturbances of Contractility." As in the case of the discussion on auricular fibrillation, the different theories of its production are given fairly and impartially, just how much so depending on the views of the reader.

The book is of value to students and clinicians. There is a full bibliography.

It may not be amiss to voice the regret that more students do not have the reading knowledge of foreign languages to make such volumes as useful to them as they should be.

GESUNDHEITSPFLEGE IM MITTELALTERLICHEN BASEL. By PROF. KARL BAAS, M.D.  
Pp 120. Zurich. Füssle, 1926.

DIE STAATLICHE PESTPROPHYLAXE IM ALTEN ZÜRICH. DR. ARNOLD TREICHLER.  
Pp 28. Zurich. Füssle, 1926.

Both treatises, which form part of a series of studies dealing with the local medical history of Zurich edited by Dr. Wehrli, offer a vivid picture of medieval medicine and the gradual development of state control of epidemics and public health in general. The treatise of Baas is particularly rich in material relating to the guild organization of the surgeons, the regulation of midwives and the development of the city hospitals. Both studies will form an interesting addition to the medico-historical library.

LES MÉDICAMENTS CARDIAQUES. By L. CHEINISSE. Price, 14 francs. Paris.  
Masson et Cie, 1925.

Dr. Cheinisse has collected a vast amount of information from the literature of all countries, has sifted and analyzed the facts given, and in this volume gives the present status of all of the drugs used in the treatment of cardiac disease.

He considers in turn the source of the medicine, its various preparations and modes of administration with a critical discussion of their indications and relative values, the indications and contraindications for use of the drug itself, its therapeutic, pharmacologic and physiologic effects and its effects when administered with other drugs.

He considers digitalis, strophanthus (strophanthine and ouabain), squills, sparteine, adonis vernalis, as well as several less known drugs, as specifics, and calcium chloride, caffeine, camphorated oil, epinephrine, atropine, eserine, quinine and quinidine as adjuncts, ending with chapters on cardiac opotherapy and intracardiac injections.

The book is simply and clearly written, and accomplishes well the aims of the writer.

## EFFECT OF ULTRAVIOLET LIGHT ON OXYGEN CONSUMPTION AND ON TOTAL METABOLISM

EDWARD H. MASON, M.D.

MONTREAL

AND

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The effect of ultraviolet light on the physiologic functions of the cell is a problem of fundamental importance. One of these functions is that of cellular respiration and heat production. In this article are reported experiments made to determine whether the total metabolism of the human organism is affected by maximum exposures of ultraviolet light from a quartz mercury vapor lamp.

The earlier work of K. A. Hasselbalch on animals and that of A. DuRoi on man would indicate that light has little effect on the total metabolism. The opinion of clinicians employing ultraviolet irradiations therapeutically is that this form of wave length results in a stimulating action. However, there are few exact measurements. Harris<sup>1</sup> has found that the full irradiations from a quartz mercury vapor lamp are without appreciable effect on the total metabolism as judged from carbon dioxide production over short periods of time, while the ultraviolet rays alone, obtained by a filter of blue violet glass with a transmissibility from 291 to 436 millimicrons, exert an early stimulant action on gaseous metabolism. In a series of four white rats, the carbon dioxide production increased appreciably during the first fifteen minutes of application, falling to the basal level during the second fifteen minutes, subsequently it fell to a little below the basal level. Approximately the same increase in carbon dioxide production was obtained in two light gray rats exposed to the filtered irradiations from an iron arc (wave length, from 291 to 436 millimicrons). The neutralizing effect of the longer wave lengths on the shorter ones was observed by Mme. and M. V. Henri<sup>2</sup> in their studies on the slowing of protoplasmic movement.

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† This work was originated at the suggestion of H. H. Mason of New York, and was carried out in Montreal.

1 Harris, D. T. Proc. Roy. Soc. Biol. Sc., Series B, 98:171, 1925.

2 Henri, Mme. V., and Henri, V. Etudes de Photochimie Biologiques, 1912.

in unicellular organisms, and by Hill<sup>3</sup> when carrying out similar studies with infusoria

It is well known that buckwheat (*Fagopyrum esculentum*) contains a substance, phytoporphyrin, which can photosensitize animals and human beings. This phenomenon has been observed most commonly among swine and sheep, and occasionally in cattle and goats. White or spotted animals are susceptible, while black ones are protected. The sensitization is greater if the buckwheat is eaten during the blooming period. The mechanism of this phenomenon is not well understood. It would appear to be similar to that following the injection of hematoporphyrin. Harris<sup>1</sup> has suggested that when hematoporphyrin is acted on in the superficial layers of the dermis by ultraviolet light, it forms some derivative which is toxic, and which is transported by way of the circulation. Melanin in the skin protects against the contact of the ultraviolet light with the photosensitive substance, because it converts the short rays into longer ones. The theory that the toxic conversion product is transported throughout the body is supported by the fact that a white sensitized rat dies in a few minutes when exposed to such short rays (wave length, from 291 to 436 millimicrons), and that at autopsy the main lesion is found to be pulmonary edema and hemorrhage.

Experiments have been performed on man in this clinic to determine whether the mixed rays from a quartz mercury vapor lamp have an effect on oxygen consumption and heat production.

#### METHODS

In the earlier cases, the oxygen consumption alone was determined, but in the majority the total metabolism was ascertained. In the former, oxygen consumption alone was recorded and a Sanborn Benedict closed circuit apparatus was used. In those in which the total metabolism was determined the expired air was collected in a Douglas bag, and analyzed in duplicate on a modified Henderson-Haldane machine.

No attempt was made to filter off the longer wave lengths, thus, the patients were exposed to a rich source of ultraviolet light mixed with considerable visible light. Two lamps were used, a modern Burdick and a Hanovia, both were quartz mercury vapor instruments, air cooled and operated at 75 volts on a direct current of 110 volts. The exposures were general, being given equally on the front and the back of the body, and were forced to the maximum dosage that the patient could endure. Marked erythema was produced in all cases and in those in which there were repeated exposures to light extensive pigmentation followed. Throughout the experimental periods all the patients were in the hospital ward, and great care was taken that the basal state was

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3 Hill, L. Sunshine and Open Air, London, 1924 Edward Arnold

maintained throughout the determinations of metabolism. The diet was controlled only in a case of pernicious anemia (experiment 6, chart 6), in which the patient received a high iron diet. In cases in which a metabolism test and a light exposure were made on the same day, the former preceded the latter. In the accompanying table and charts the actual light dosage received was twice the amount stated, as the single dose was applied equally to both sides of the body.

#### EXPERIMENTAL OBSERVATIONS

Studies have been conducted in ten cases, and eight of these patients have shown a notable lowering of heat production. This decrease in

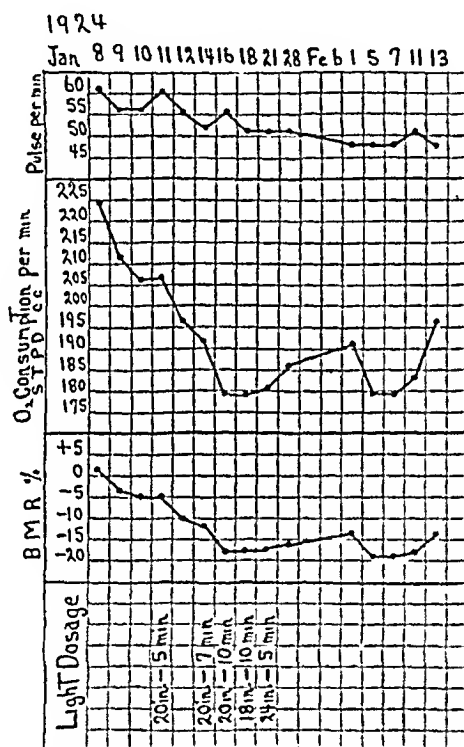


Chart 1 (case 1)—Effect of ultraviolet light on a patient with fibrinous pleurisy

total metabolism has been associated with a slowing of the pulse rate. In no case has an increase of metabolism been found.

The subjects who have reacted to exposures of ultraviolet light with a lowering of their total metabolism may be classified in two groups: group I, normal persons in whom there is a satisfactory production of pigment, and group II, persons who have an increased quantity of circulating bilirubin.

*Group I*—This group includes five cases (charts 1 to 5). The decrease in heat production varied directly as the degree of pigmentation. In experiments 1, 2 and 3 (charts 1, 2 and 3) in which a marked skin pigmentation developed due to a prolonged course of light exposures